

**CONTACT MAINTENANCE STRATEGIES AND
BRIEF PSYCHOTHERAPEUTIC INTERVENTIONS
FOR SUICIDE PREVENTION:
AN IMPLEMENTATION, EFFECTIVENESS, AND
COST-EFFECTIVENESS STUDY**

**ESTRATEGIAS DE MANTENIMIENTO DE
CONTACTO E INTERVENCIONES
PSICOTERAPÉUTICAS BREVES PARA LA
PREVENCIÓN DEL SUICIDIO:
ESTUDIO DE IMPLEMENTACIÓN, EFECTIVIDAD
Y COSTE-EFECTIVIDAD**

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**Estrategias de mantenimiento de contacto e
intervenciones psicoterapéuticas breves para la
prevención del suicidio: estudio de
implementación, efectividad y coste-efectividad**

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psychotherapeutic interventions for suicide
prevention: an implementation,
effectiveness, and cost-effectiveness study**

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Lo cierto será siempre penúltimo

y lo último siempre será incierto

*(What is certain will always be penultimate
and what is ultimate will always be uncertain)*

Pedro Laín Entralgo

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1. Overall abstract

Suicide is a leading cause of death. Non-lethal suicidal behavior, the single most salient risk marker of future death by suicide, is a major reason for emergency medical care with an increasing incidence globally. Reversing this trend constitutes a crucial public health challenge. The period following a suicide attempt entails great reattempt risk, hence providing an opportunity window for individual-level suicide prevention efforts. Most post-discharge suicide prevention interventions seek to bolster contact between suicide attempters and mental health providers, in order to reduce the sense of social isolation and increase treatment compliance with outpatient visits and treatments. Psychotherapeutic interventions can also prevent suicidal behaviors among recent attempters. However, whether psychotherapy provides additional value as compared to simpler, less costly, and more practicable contact interventions remains partially unanswered. This real-world study evaluated three post-discharge suicide prevention interventions currently in use in the Community of Madrid, Spain. First, we estimated the degree of implementation and effectiveness of the Suicide Risk Prevention Program (ARSUIC is its Spanish acronym), an emergency-department scheduled priority visit at an outpatient clinic within one week after hospital discharge that is currently considered treatment as usual throughout Madrid. We found that, compared to the previous standard of care, ARSUIC reduced time between discharge and first visit an average 1.5 days, and lowered the risk of suicide re-attempt by 24% over a three-year follow-up. Then, we compared ARSUIC to two augmentation strategies based on increased telephone and in-person brief contacts (Enhanced Contact) and on 8 sessions of individual problem-solving therapy (Psychotherapy), finding that both outperformed ARSUIC by an additional 40% risk reduction over a one-year follow-up. The difference in effectiveness between Enhanced Contact and Psychotherapy was negligible. Last, we compared the three interventions in terms of cost-effectiveness, finding that both augmentation strategies are probably cost-effective, in comparison to ARSUIC, under a variety of possible scenarios, and that Enhanced Contact attained similar effectiveness at a slightly lower cost than Psychotherapy. Further research is warranted to identify the predictors of success for each of the studied interventions: although contact interventions seem the most efficient choice of treatment for an unselected sample of high-risk individuals, certain subtypes of patients may benefit greatly from individual psychotherapy.

Keywords: suicide, suicide attempt, self-harm, suicide prevention, implementation science, target trial, comparative effectiveness and outcomes research, cost-effectiveness, real-world data, brief contact interventions, problem-solving psychotherapy

1. Resumen general

El suicidio es una de las principales causas de muerte. La conducta suicida no letal, el más relevante marcador de riesgo de futura muerte por suicidio, es un motivo destacado de urgencia médica con una incidencia en aumento globalmente. Invertir esta tendencia es un desafío crucial para la salud pública. El periodo que sigue a un intento de suicidio conlleva gran riesgo de reintento y supone una oportunidad para la prevención individual. La mayor parte de las intervenciones a este nivel buscan aumentar el contacto entre el paciente y el profesional de salud mental, para reducir la sensación de soledad y aumentar el cumplimiento terapéutico con las consultas ambulatorias y tratamientos. La psicoterapia también previene las conductas suicidas después de un intento. Sin embargo, no está claro si la psicoterapia genera valor añadido al de intervenciones de contacto, más simples, baratas y viables. Este estudio de mundo real evaluó tres intervenciones para la prevención del suicidio al alta actualmente instauradas en la Comunidad de Madrid. Primero, estimamos la implementación y efectividad del Programa de Atención al Riesgo Suicida (ARSUIC), una visita ambulatoria durante la semana posterior al alta, programada desde el servicio de urgencias, considerada actualmente el tratamiento habitual en Madrid. En comparación con el estándar previo, ARSUIC redujo el tiempo entre el alta y la primera cita ambulatoria 1,5 días de media, disminuyendo el riesgo de reintento un 24% durante un seguimiento de tres años. A continuación, comparamos ARSUIC con dos estrategias de intensificación basadas en contactos añadidos telefónicos y presenciales (Contacto Aumentado) y en 8 sesiones de terapia de resolución de problemas individual (Psicoterapia). Ambas superaron a ARSUIC, con una reducción de riesgo adicional del 40% en un seguimiento de un año. La diferencia de efectividad entre Contacto Aumentado y Psicoterapia fue insignificante. Finalmente, comparamos las tres intervenciones en términos de coste-efectividad. Ambas estrategias de intensificación resultaron probablemente coste-efectivas, en comparación con ARSUIC, considerando una variedad de escenarios potenciales, y Contacto Aumentado logró similar efectividad con un coste ligeramente menor que Psicoterapia. Es preciso identificar predictores de éxito para cada intervención: si bien las intervenciones de contacto parecen más eficientes para una población no seleccionada, algunos subtipos de pacientes pueden beneficiarse considerablemente de psicoterapia individual.

Palabras clave: suicidio, intento de suicidio, autolesiones, prevención, ciencia de implementación, ensayo ideal, investigación comparativa de efectividad y resultados, coste-efectividad, datos del mundo real, intervenciones breves de contacto, psicoterapia de resolución de problemas

2. Introduction

Abstract

Suicide, a major public health concern, takes around 800 000 lives globally every year. Attempted suicide, the most faithful risk marker of future suicide, is a leading cause of emergency care with a rising incidence. Prevention strategies for suicidal behaviors can be implemented at the population and the individual level. For high-risk individuals, most psychosocial prevention interventions seek to either enhance contact maintenance with mental healthcare providers or use manualized psychotherapy to improve the patient's ability to cope with triggers of suicidal crises. Although several of such strategies have been deployed throughout the Community of Madrid, to date no study has evaluated their actual performance systematically. The following section describes recent trends in suicide and non-lethal self-harm globally and in Spain, reviews the existing evidence regarding suicide prevention strategies from a multi-level framework, and provides a justification to the real-world comparative study of contact maintenance and psychotherapeutic interventions for individuals at high risk of suicide.

Resumen

El suicidio, un problema principal de la salud pública, se lleva cerca de 800 000 vidas globalmente cada año. El intento de suicidio, el marcador más fidedigno de futuro riesgo de suicidio, es una de las principales causas de tratamiento urgente y tiene una incidencia en aumento. La prevención del suicidio se puede ejercer en los niveles poblacional e individual. Para individuos con alto riesgo, la mayor parte de intervenciones psicosociales buscan aumentar el contacto con los profesionales de salud mental o utilizar psicoterapias manualizadas para mejorar la habilidad del paciente para afrontar los disparadores de las crisis suicidas. Aunque varias de estas intervenciones han sido implementadas en la Comunidad de Madrid, ningún estudio ha evaluado sistemáticamente su rendimiento real. Esta sección describe las tendencias recientes de suicidio y conducta suicida no letal globales y en España, revisa la evidencia sobre estrategias de prevención del suicidio desde una perspectiva multinivel, y justifica el estudio comparativo de mundo real de las intervenciones basadas en contactos y en psicoterapia para individuos con alto riesgo de suicidio.

2.1 Suicide and non-fatal self-harm: a major public health concern

2.1.1 Global trends in suicide

Suicide, the “only one really serious philosophical problem” (Camus, 1955), is a major public health concern that takes around 800 000 lives globally every year. Death by suicide is the second leading cause of death among youth, and accounts for 57% of all violent deaths and

roughly 1.5% of all mortality - more than malaria or breast cancer (World Health Organization, 2019). Because suicide “is of all modes of death that which leaves in the hearts of the sorrowing survivors the most poignant and the most enduring sting” (Wade, 1879), its impact on families and communities is far-reaching: grief, stigma and subsequent increases in psychiatric conditions and suicide rates reverberate over generations.

Suicide ranks currently as the 18th leading cause of death worldwide – second in ages 15 to 29 and third in ages 15 to 45 (WHO, 2019). Given the fact that considerable limitations exist in the detection and registration, the number of deaths by suicide are likely underestimated (WHO, 2014; AbouZahr et al., 2015). While a recent study suggests that the global age-standardized mortality rate due to suicide has decreased by 32.7% between 1990 and 2016 (Naghavi, 2019), trends in suicide rates vary substantially between countries. From 195 countries included in Naghavi’s analysis, 63 registered noticeable decreases, 132 reported not significant differences and only 8 increases in suicide rates (2019). Notably, substantial declines in China (-64.1% decrease in age-standardized suicide mortality rate between 1990 and 2016), a country that had constant increases in suicide rates between years 1900 and 1970 (Phillips et al., 2002), and India (-15.2% decrease) drive most of the global decrease in suicide rates, given that these two countries account for approximately 36% of the world population (United Nations, 2017) and 44.2% of deaths by suicide globally in 2016. The countries with the highest observed recent increases in suicide rate are Zimbabwe (+96.2%), Jamaica (+70.9%), Paraguay (+70.4%), Uganda (+61.6%), several Western sub-Saharan African countries like Liberia (+45.9%) or Cameroon (+37.6%), and Mexico (+35.6%).

Interestingly, the estimated global male to female ratio in suicide has seemingly increased in the recent decades from 1.40:1 in 1990 to 2.17:1 in 2016 (Naghavi et al., 2019), and suicide mortality between ages 15 and 19, an age stratum where females traditionally displayed higher suicide rates, shows now virtually no age-specific differences (Rhodes et al., 2014; Wasserman et al., 2005). Age distribution of suicide mortality varies considerably across the globe, but it generally distributes in a bimodal fashion, peaking first around adolescence and again in adults

over 70 years of age. There are noticeable differences between low/middle- and high-income countries in this respect. Middle-aged males have higher suicide rates in high income countries than their counterparts in low and middle-income countries, where suicide rates are higher among adolescents and elderly females (WHO, 2014).

2.1.2 Global trends in non-fatal self-harm

Global non-fatal self-injury rates are difficult to study since no international entity has been able to maintain a systematic registry, and most nationwide or international suicide statistic reports do not include information on non-lethal self-injury (WHO, 2014). Based on data available from both regional studies using medical records or surveys and from the World Mental Health Surveys conducted in 21 countries between 2001 and 2007 and using the WHO Composite International Diagnostic Interview (CIDI) (Nock, 2012; Kessler et al., 2008), WHO estimates that over 20 suicide attempts take place globally for each death by suicide (WHO, 2018).

However, the number of estimated suicide attempts, as well as the relationship between attempted and completed suicide, varies remarkably across countries. For example, while the United States reported around a 5% 12-month prevalence of suicide attempts, in Italy, the prevalence was just 0.5% for the same time period (Borges et al., 2010). Further, Spain reports 174.4 attempts per death by suicide, a figure that lowers to 64.1 in Italy (Blasco-Fontecilla et al., 2018). Of note, Blasco-Fontecilla et al. have recently proposed the use of a ratio between attempted and completed suicides across countries as a means of evaluation of health care delivery for people at high risk of suicide (2018).

2.1.3 Trends in suicide and non-fatal self-harm in Spain

Spain has traditionally shown one of the lowest rates of suicide among Western European countries, in line with other Mediterranean countries, with around 12 suicides per 100,000 inhabitants in men and 4 in women (Instituto Nacional de Estadística, 2019). Notwithstanding, suicide is the most frequent cause of death among the youth and, although there has been

substantial debate regarding whether there have been recent increases in the national rates (Ayuso-Mateos, 2013), it seems now plausible that such increases can be detected at least among women (Cayuela et al., 2018) and, in particular, immigrant women (Martínez-Alés et al., 2019a). Given the lack of a faithful national registry of self-harm, there is no clear consensus as to whether self-harm is on the rise in Spain. However, some studies suggest that this is the case: the number of telephone calls related to suicide attempting that were made to the emergency healthcare system of a region in Andalusia, Spain, increased steadily between 2010 and 2013 (Mejías-Martín et al., 2017). In addition, despite the important limitations that suicide attempts entail for accounting practices in nationwide electronic healthcare records based on ICD coding, data from Spain's hospital discharge database indicate annual increases in the number of diagnoses indicating self-harm (ICD-9-CM E-950 codes) between 2010 and 2015 (Ministerio de Sanidad, Consumo y Bienestar Social, 2018).

2.2 Suicide prevention: an unmet clinical need

2.2.1 A multi-level approach to suicide risk factors

There is substantial evidence that certain characteristics are associated (causally, in most cases) with a higher risk of suicidal behaviors. These risk factors, that can be classified in biological, behavioral and social (Chan et al., 2016; Franklin et al., 2017), interact in complex hierarchical networks (O'Connor & Nock, 2014). Mental disorders are considered among the strongest predictors (Holmstrand et al., 2015). For instance, suicide is 20 times more likely if a previous diagnosis of major depression is present. Suicide is also associated to bipolar disorder, drug and alcohol addiction disorders and psychoses, as well as to a broad variety of social stressors, such as socioeconomic disadvantage and the lack of social support (Bertolote et al., 2002).

It should be noted that suicide rates are determined, at least partially, by causal factors that affect entire societies and thus operate beyond the level of the individual, but impact individuals within those societies (Martínez-Alés & Keyes, 2019b). Emile Durkheim's seminal book *Le Suicide* captured these "(causes) of suicide as a collective phenomenon", "whose action is felt

by society as a whole” (1966). Geoffrey Rose discussed such population-level effects when discussing blood pressure with “why some individuals have high blood pressure is a different question than why some populations have more burden of high blood pressure?” (2001). Echoing Durkheim and Rose’s work, while we term “individual-level factors” those that predict who will die by suicide and who will not within a population, we also term “group-level factors” as those that predict which populations will have higher or lower suicide rates. Over the 20th century, these group-level factors have been commonly used to explain health outcomes in psychiatric epidemiology: Morris referred to this as the “ecology of mental disorders” in his *Uses of Epidemiology* (1957). For instance, in a classic study, Faris and Duhham described a direct correlation between level of urbanicity and rate of schizophrenia in Chicago (1939), a finding that lead to a century of hypotheses and empirical data analysis regarding environmental risk factors of psychotic disorders (Susser & Martínez-Alés, 2018; Plana-Ripoll et al., 2018).

Mervyn Susser coined the term “integral variables” (1994a) to refer to variables that are shared by a whole social group, such as economic downturns or urban dwelling. By definition, a comparison between individuals who comprise the target social group will not allow to estimate the causal effect of an integral variable. Instead, ecologic designs that consider the whole group as a legitimate unit of analysis and perform between-groups comparisons are required (Susser, 1994b; Susser, 1973). In words of Durkheim, “the social rate must be taken directly as the object of analysis” (1966). For example, the 10-fold difference in suicide rates between Lithuania or Russia and Peru or Lebanon (Naghavi et al., 2019) can illustrate the need of the conceptualization of suicide using an ecological perspective. Similarly, remarkable differences can be found across countries within Europe (Organization for Economic Co-operation and Development, 2019), states and regions within the United States (Centers for Disease Control, 2018) or areas within the city of London (Rezaeian et al., 2005). Such variation prompts questions about how a region’s political, socioeconomic and cultural context might impact suicide risk (Martínez-Alés et al., 2019c)

Notwithstanding, traditional and innovative risk prediction tools have characteristically approached suicide from an individual-level perspective (Roy et al., 1982; Ursano et al., 2014; Vahabzadeh et al., 2016); and may be overlooking central determinants of risk that include country-level and area-level social and political factors, such as general area industry and employment, past suicide rates in the geographic area, and economic growth and contraction (Fountoulakis et al., 2016). Further, beyond geopolitical concerns are actual environmental factors that influence risk, including temperature, elevation, both synthetic and natural chemical exposures, and other topographical and toxicological features of the physical environment (Deisenhamer, 2003; Akkaya-Kalayci et al., 2017; Fountoulakis et al., 2016).

2.2.2 The importance of suicidal behaviors

Non-lethal suicidal behaviors are considered the most specific risk marker for death by suicide (Turecki & Brent, 2015; Arias et al., 2016). Some researchers find that these behaviors may involve almost 30 times more incidence of accomplished suicide (Finkelstein et al., 2015). Addressing suicidal behavior, therefore, offers a great opportunity to prevent future suicide attempts and, accordingly, substantial attention has been directed towards individuals who engage in non-lethal suicidal behaviors.

Moreover, suicidal behaviors and non-lethal self-harm constitute a leading reason for emergency medical care on their own, driving high direct medical costs (Czernin et al., 2012) and generating over \$93 billion in total burden per year, only in the US (Shepard et al., 2016) – roughly a 1.36% of the total disability-adjusted life years globally (Global Burden of Disease, 2019). As mentioned, recent reports suggest that the incidence of suicidal behaviors is increasing globally (Olfson et al., 2017) and in Spain (Mejías-Martín et al., 2017). Reversing this trend constitutes a major public health challenge.

2.2.3 Population-level interventions to reduce suicide risk

Several population-level interventions have proved effective for suicide risk reduction. In general terms, they fall within three main categories: education campaigns, regulations in mass

media coverage and restriction of access to means. Among evidence-based educational approaches, we would like to highlight the implementation of school-based programs for suicide prevention (Zenere et al., 1997; Wasserman et al., 2015) and “gatekeeper training” strategies, directed towards individuals who have high probability of contacting suicidal individuals but are not designated specifically as mental health professionals, such as teachers or general practitioners (Isaac et al., 2009).

Media reporting of high-profile suicides has a large evidence base as a causal catalyst to subsequent increases in population level suicide rates (Sisask et al., 2012; Pirkis et al., 2006; Fink et al., 2018). This phenomenon is sometimes referred to as the “Werther effect”, after the protagonist of a 1774 German novel who dies by suicide, prompting so-called “copy-cat” suicides reported throughout Europe at the time. Increases in suicide after wide-spread media coverage of a suicide event are framed within the broader behavioral contagion theory (Gould, 2001). Notably, recent studies point out the importance of the social context at shaping the harmful, neutral or protective impact of suicide media portrayals (VanderWeele et al., 2019). Opportunities for effective suicide prevention at this level generally consist on a variety of reporting recommendation guidelines seeking to enhance responsible, non-sensationalist coverage of suicide and related events (American Association of Suicidology, 2019).

Mass media also plays a role in the regulation of a population’s “cognitive-access” to suicide means and methods (Florentine et al., 2010; Fink et al., 2018). However, the term “means reduction” usually refers to evidence-based interventions aimed at preventing the population from physically accessing potentially lethal means (e.g. Gunnell et al., 2003; for a review, see Pirkis et al., 2015). This approach builds on empirical studies providing a substantial body of evidence that ease of access greatly impacts the risk of attempting suicide (Marzuk et al., 1992) and the method choice (Eddleston et al., 2006), especially in impulsive suicidal behaviors - the most frequent type (Hawton et al., 2013). Of note, Deisenhammer et al. estimated that half of suicide attempt survivors report an interval between the onset of a serious suicidal thought and subsequent suicide attempt of 10 minutes or less (2009).

While reductions in access to lethal means is associated with lives saved, there remains concern about substitution of method as an additional risk for suicide. Indeed, reducing the access to lethal means is more effective if an alternative method available for substitution has a lower associated lethality – this can be due to a higher ability to abort mid-attempt or to a lower inherent deadliness. Firearms, present in almost 33% of homes in the US and in 51% of total suicides in the US, entail 50 times the potential lethality of drug overdose (Marzuk et al., 1992). A range of epidemiological studies have confirmed higher suicide rates in states with higher gun ownership levels (Miller et al., 2007), and higher suicide risk for people living in a household with firearms (Brent et al., 1993; Kellermann et al., 1992).

In sum, the contribution of population-level causes of suicide is significant, and in terms of their potential to reduce the burden of harm, quite influential when taken seriously. As suicide prevention efforts continue, a sustained and serious focus on population-level effects is critical.

2.2.4 Individual-level interventions to reduce suicide risk

The key first step to suicide risk prevention at the individual level involves the detection of individuals at high risk of suicidal behaviors based on the abovementioned risk factors (Hernández-Calle et al., 2020). The healthcare setting is considered adequate for risk detection, since up to 45% who die by suicide have been seen by a physician during the previous month. For instance, Emergency Departments (ED) can play a key role in such strategies: suicide attempters treated at the ED frequently repeat self-harm during the following year (Olfson et al., 2017) and a single ED visit for self-harm increases future suicide risk nearly 6-fold (Owens et al., 2005). In addition, suicidal ED patients have low rates of outpatient treatment engagement (Lizardi & Stanley, 2010). Hence, there is a growing interest in interventions initiated at the ED (Arias et al., 2016).

The referral of high-risk individuals to general mental health services following risk detection (Van der Feltz-Cornelis et al., 2011) is another key step to address suicidal risk. There is also extensive literature on interventions that specifically target suicidality among high-risk

individuals, as evidence indicates that programs directly addressing suicidal behaviors (Meerwijk, 2016) entail additional benefits to those of receiving general mental healthcare. Indeed, several clinical interventions are effective at lowering suicide risk among individuals classified as high-risk and, accordingly, they are considered best practice in psychiatry (Zalsman et al., 2016). For example, in terms of pharmacotherapy, there is consensus that suicidal patients with schizophrenia and bipolar disorder benefit, respectively, from receiving treatment with clozapine and lithium carbonate (Meltzer et al., 2003; Goodwin et al., 2003).

The following section reviews the current evidence on psychosocial interventions aimed reducing suicide risk among high risk individuals detected at the healthcare setting. In particular, we focus on suicide risk reduction among suicide attempters, a clinical subgroup with markedly high risk of suicide.

Given that the first weeks following an attempted suicide entail an exceptionally high reattempt risk (Owens et al., 2002; Parra-Urbe et al., 2017), they offer a critical opportunity for indicated tertiary prevention. Several high-risk case-management programs focus on enhancing patient engagement and contact with mental health providers, favoring access to medical resources after discharge through contact maintenance strategies (Mann et al., 2005; McMMain et al., 2017). The rationale behind contact interventions is twofold. First, regular contacts reduce the sense of social isolation, one of the main risk factors for suicidal outcomes (Calati et al., 2019). Second, as mentioned, patients who engage in suicidal behaviors often experience barriers to access to proper care, and frequently disengage from follow-up visits (Lizardi & Stanley, 2010). Personal contacts provide emotional support, increase treatment compliance with outpatient visits and medications and enhance the odds that the patient will seek help in the event of a new suicidal crisis. In a pioneer randomized trial including 843 suicide attempters who did not engage in follow-up treatment, Motto and Bolstrom assigned half of participants to receive personalized letters over the following 5 study years (2001). After just two years, the suicide rate among the control group doubled that of those assigned to the intervention. Variations of this approach include the use of short text messages, postcards, telephone calls, et cetera (Hassanian-

Moghaddam et al., 2011; Cebria et al., 2013; Vaiva et al., 2018). The Safety Planning Intervention is an interesting evidence-based augmentation of brief contact strategies that is widely implemented across the globe that seeks to reduce the patient's access to lethal means, prioritize the most adequate coping strategies during suicidal crises and enhance outreach to mental health providers (Stanley et al., 2012).

Manualized psychotherapies, including problem-solving (McLeavey et al., 1994) cognitive-behavior (Brown et al., 2005), dialectical-behavior (Linehan et al., 2006), or psychodynamic therapy (McMain et al., 2017) are also seemingly effective. However, psychotherapy for suicide behaviors has been called into question when compared to more feasible programs aimed at simply favouring continuation of care after discharge: an emerging body of literature suggests that evidence-based psychotherapeutic treatments do not outperform contact maintenance. In a recent RCT meta-analysis, the WHO Brief Intervention and Contact (BIC), a program of 9 follow-up contacts significantly lowered the odds of suicide after an attempt by 80% (OR=0.20, 95% CI = 0.09-0.42), whereas Cognitive-Behavioral Therapy (CBT) did so by 66% (OR=0.34, 95% CI 0.12-1.03) (Riblet et al., 2017). A common misunderstanding of this widely cited meta-analysis is that psychotherapy does not reduce suicide risk “significantly” among high-risk individuals. However, this interpretation is incorrect due to at least two reasons (Martínez-Alés et al., 2019d): first, conflating statistical significance with decision-making is prone to errors (Greenland et al., 2016); and second, most trials compared CBT to some safety planning or contact maintenance intervention, while the WHO BIC was, in turn, compared to treatment as usual in several settings where no suicide-specific intervention is standard: comparing any intervention to an effective intervention can be challenging and yet the meta-analysis found over a 60% risk reduction. As a result, the question whether individualized psychotherapy generates additional benefits compared to a schedule of brief contact interventions remains unanswered.

2.2.5 Using real-world data to inform decision-making

Generating evidence that informs clinical and decision-making efficiently can pose additional methodological challenges. Randomized trials, widely viewed as the gold-standard study design to test interventions in terms of efficacy and safety, have been called into question regarding their ability to yield effectiveness estimates that are transportable to the target population where the study sample was drawn from, or to populations with different characteristics (Deaton and Cartwright, 2018). Although randomization generates comparison groups that, absent errors, can be viewed as comparable in expectation, whether the evidence generated by these highly internally valid designs is readily applicable for real-world decisions depends on the extent to which the conditions of the trial resemble those of the target population. In addition, critics argue that, for psychotherapeutic interventions, comparative effectiveness estimated obtained from randomized trials are “inappropriate, and sometimes impossible” (Bothwell et al., 2016), because of the inherent difficulty to assign participants at random to a highly individualized intervention that may be tailored to the client increasingly over time. Also, many trials have excluded suicidal individuals systematically over the last decades due to bioethical tensions that can be difficult to overcome (Oquendo et al., 2004).

As a result, there is a growing call for comparative effectiveness estimates obtained from data from the clinical practice that can either complement the information obtained from randomized designs, by providing key insights for transportability and, in general terms, a greater external validity (Sherman et al., 2016); or emulate the ideal target trial when randomization is unfeasible due to technical or bioethical reasons (Hernán et al., 2016).

2.2.6 The need for cost-effectiveness estimates

Another key aspect in for the development and scaling-up of effective interventions for suicide risk is conducting economic evaluations. According to the World Health Organization, conducting accurate economic evaluations of interventions for suicidal behaviors is essential for the development of suicide prevention strategies (2014). Cost-effectiveness studies are

particularly useful to assist resource prioritization in service planning, because they help identify treatment alternatives that “optimally allocate resources to maximize health gains” (Bernecker et al., 2019). Nevertheless, there is very limited good quality information published on the cost-effectiveness of interventions for suicide prevention (Bustamante Madsen et al., 2018). Thus far, no study has conducted a comparison in terms of cost-effectiveness between a brief contact intervention and a psychotherapeutic program.

2.3 Individual-level suicide risk prevention in the Community of Madrid

The Community of Madrid’s Regional Office of Mental Health established suicidal behavior prevention as a priority in its 2010-2014 Mental Health Strategy. This implied to launch the Suicide Risk Attention Program (ARSUIC is its Spanish acronym). Its main purpose is to offer priority specialized care to those patients who have attempted suicide, in order to prevent potential relapses. Even though ARSUIC is a multi-faceted program that includes several interventions at different levels (Comunidad Autónoma de Madrid, 2019), the current study uses the term “the ARSUIC intervention” to refer to a priority appointment with an outpatient psychiatrist, within 7 days following discharge after a suicide attempt. Additionally, other Psychiatry Departments of the Community of Madrid deployed program augmentations that include either the implementation of an enhanced contact strategy or of individual problem-solving psychotherapy.

2.3.1 The ARSUIC intervention

The Suicide Risk Attention Program (ARSUIC, by its Spanish acronym) seeks to ensure a prioritized and specialized care for those individuals who have attempted suicide, fostering potential contacts with mental health workers during the more dangerous first days after the attempt. It was implemented across the Community of Madrid during the last trimester of 2012. Previously, priority specialized appointments could take up to 19 days (Comunidad Autónoma de Madrid, 2017). The program considers that every suicide attempter must have an appointment

with a general psychiatrist with no specific suicide prevention training within the first 7 days after hospital discharge. Hence, it does not imply any specific contact maintenance strategy or therapeutic intervention other than scheduling a priority outpatient visit in the next 7 days. The date and time of the appointment is explained to the patient and indicated in the hospital discharge report by the ED psychiatrist or, if the patient has been admitted to the hospital, by the treating psychiatrist. Following the priority appointment, the patient continues the usual psychiatric care; no further follow-up contacts are used, and no specific materials are shared. No new staff has been hired to conduct the program; instead, every community psychiatrist should devote a number of weekly consultation hours to the program.

2.3.2 The Enhanced Contact intervention

Participants from Madrid's western catchment area received an enhanced contact maintenance intervention framed within the greater "Código 100" Suicide Prevention Program, a strategy delivered in collaboration with Madrid's extra-hospitalary emergency service in order to guarantee an appropriate continuity of care (López-Castroman et al, 2015a). Inclusion criteria to "Código 100" are: to have attempted suicide, to be 18 y-o or older and to sign an informed consent form. The intervention starts with an appointment 3 days after discharge, followed by 6-12 months of an intensified frequency of outpatient visits, depending upon the patient's severity and his/her personal preference, with a specifically devoted psychiatrist trained in suicide prevention. In addition, every patient receives telephone calls from the hospital at follow-up months 1, 6 and 12. The content of these calls was explanatory and supportive, seeking to reassure patients, clarify their doubts regarding treatment, enhance their adherence to follow-up visits and remind them of the available emergency treatment options in case of a new crisis. It does not include a specific psychotherapeutic approach. Then, the patient continues usual treatment at a CMHC.

2.3.3 The Psychotherapy intervention

Participants from Madrid's southern catchment area received a modified ARSUIC intervention, adding individual psychotherapy. Inclusion criteria are to have attempted suicide, to be 18 y-o or older and not to have a concurrent ongoing therapeutic treatment at an outpatient clinic. The psychotherapy is held at the General Hospital. It includes 2 months of weekly, 30-minute-long individual, non-suicide-specific therapy sessions, focused on problem-solving, stress reduction and cognitive reformulation. Therapy sessions are conducted by trained clinical psychologists, under a general psychiatrist's supervision. Then, the patient is referred to a General Practitioner (GP) or a CMHC. In case the participant fails to attend the sessions, reminder telephone calls are made from the hospital.

2.3.4 Justification of the study

The ARSUIC intervention was implemented globally throughout all healthcare catchment areas of the Community of Madrid. However, no prior study has evaluated the actual uptake and impact of the program in the clinical setting, in terms of its effective implementation lowering the average time between discharge and the first outpatient visit or its effectiveness lowering the risk of suicidal behaviors among suicide attempters. Also, other catchment areas deployed additional augmentations based on contact maintenance strategies or psychotherapy, but no study has assessed whether these strategies are in fact more effective compared to the ARSUIC intervention, which of the two augmentation approaches is comparatively more fruitful and, last, which intervention has the highest probability of being cost-effective and at which level of willingness-to-pay. Notably, while the ARSUIC intervention and the two augmentation strategies seem reasonable given the existing evidence, very few of the studies evaluating similar interventions have been conducted elsewhere, hence leading to reasonable doubts regarding transportability to the Spanish context, and no study has used real clinical data to obtain comparative effectiveness estimates of these interventions following a head-to-head rationale.

This dissertation to qualify as a Doctor of Philosophy includes 4 original research articles evaluating the implementation, effectiveness, and cost-effectiveness of the ARSUIC intervention and two augmentation strategies based on enhancing contact maintenance and problem-solving psychotherapy, and 8 additional research articles completed within the doctoral program that directly inform the study introduction and methods sections.

3. Objectives and hypotheses

Abstract

This study evaluated three suicide prevention strategies (ARSUIC, Enhanced Contact and Psychotherapy) currently deployed in the Community of Madrid. The overall objective was to provide decision-makers with real-world estimates of the actual uptake, effectiveness and cost-effectiveness of the interventions. First, we estimated the degree of implementation of the ARSUIC intervention, currently considered treatment as usual throughout Madrid. Then, we calculated this intervention's clinical effectiveness at lowering suicide risk among suicide attempters. Last, we estimated the comparative effectiveness and cost-effectiveness of the Enhanced Contact and Psychotherapy interventions, both in comparison to ARSUIC and comparing them head-to-head.

Resumen

Este estudio evaluó tres estrategias para la prevención del suicidio (ARSUIC, Contacto Aumentado y Psicoterapia) actualmente en uso en la Comunidad de Madrid. El objetivo general era proveer a los decisores con estimadores del nivel de adopción, efectividad y coste-efectividad de estas intervenciones en la práctica clínica real. Primero, estimamos el grado de implementación de la intervención ARSUIC, actualmente considerada el tratamiento habitual en Madrid. A continuación, calculamos la efectividad clínica de ARSUIC reduciendo el riesgo de suicidio en personas que han intentado suicidarse. Finalmente, estimamos la efectividad y coste-efectividad comparativas de las intervenciones de Contacto Aumentado y Psicoterapia, en comparación con ARSUIC y comparándolas entre ellas.

3.1 Study objectives

3.1.1 Overall study objective

The overall objective of this study was to estimate the implementation and comparative effectiveness and cost-effectiveness of three interventions for suicide prevention following hospital discharge after a suicide attempt. The three studied interventions were the Suicide Risk Attention Program (ARSUIC is the Spanish acronym), a priority appointment with a psychiatrist at an outpatient clinic within one week from discharge, scheduled at the hospital before discharge, followed by treatment as usual at the same clinic; a priority appointment with a specifically devoted psychiatrist trained in suicide prevention, within three days from discharge, followed by a flexible, individualized schedule of additional brief telephone and in-person

contacts (with at least three telephone contacts) over the following 6-month period, in tandem with treatment as usual at an outpatient clinic (this schedule is called Enhanced Contact throughout the rest of the study); and a priority appointment with a psychiatrist, at the same hospital, within one week from discharge, followed by 8 sessions of individual problem-solving psychotherapy over a 2-month period, and subsequent referral to an outpatient clinic for treatment as usual (this schedule is called Psychotherapy henceforth).

3.1.2 Specific study objectives

We conducted the following sequence of four studies, using a variety of methods for causal inference from observational data collected for healthcare and administrative purposes.

First, we estimated the actual degree of implementation and uptake of the ARSUIC intervention in the Community of Madrid. For this, we calculated the degree of fulfillment of the requirements of the intervention and analyzed changes over time in the average time between discharge and first outpatient visit following a suicide attempt in the years before and after implementation.

Second, we evaluated the clinical effectiveness of ARSUIC at reducing the risk of relapse among suicide attempters discharged from emergency departments, in comparison to treatment as usual before the deployment of the program, using a before-and-after design.

Third, we compared ARSUIC to two augmentation programs deployed in specific catchment areas of the Community of Madrid during the same period, Enhanced Contact and Psychotherapy, emulating a large clinical trial that compared individuals assigned to the three interventions over a one-year period.

Last, we used the comparative effectiveness estimates obtained in the previous step, combined with data on the real direct (medical and non-medical) and indirect costs of each interventions to estimate the comparative cost-effectiveness of TAU, Enhanced Contact and Psychotherapy from the societal perspective, to provide decision-makers with guidance for funding allocation.

3.2 Hypotheses

Our a-priori hypotheses were based on the literature on the comparative effectiveness of brief psychotherapeutic programs and contact maintenance interventions for lowering suicide risk among attempters. We hypothesized:

First, that ARSUIC would have an elevated degree of uptake, lowering significantly the average time between hospital discharge and first outpatient visit in suicide attempters, and that the degree of implementation would increase progressively over the years following program deployment.

Second, that ARSUIC would be effective at lowering the risk of relapse in suicide attempters treated at the emergency department, mainly due to a reduced risk during the time period immediately following discharge.

Third, that the two augmentation programs, Enhanced Contact and Psychotherapy, would outperform ARSUIC in terms of effectiveness at lowering suicide relapse risk and that the effect size of both interventions, in comparison to ARSUIC, would be roughly comparable.

Fourth, that the two augmentation programs, Enhanced Contact and Psychotherapy, would be cost-effective compared to ARSUIC under reasonable thresholds (i.e. those used commonly in the literature) of costs per averted suicide attempt, and that Enhanced Contact would be cost saving compared to Psychotherapy, although the increase in cost incurred by Psychotherapy in comparison to Enhanced Contact would also be negligible under reasonable thresholds.

4. Methods

Abstract

Using information retrieved from electronic healthcare records, we applied a variety of data science methods for causal inference from observational data. First, we conducted an ecological-level evaluation of the level of implementation of the ARSUIC intervention, using the time between hospital discharge and the first outpatient visit as the outcome variable. Then, we emulated two unfeasible target pragmatical trials comparing, first, participants receiving the ARSUIC intervention with a historical cohort using a mirror design and, second, participants receiving ARSUIC, Enhanced Contact and Psychotherapy, using similar ascertainment methods for the follow-up period across centers. All individual-level studies were adjusted for potential confounding using multivariable Cox regression models informed by theoretical information summarized in directed acyclic graphs. Lastly, we conducted a cost-effectiveness study, from a societal perspective, deriving deterministic and probabilistic sensitivity analyses, to inform decision-makers for funding allocation purposes.

Resumen

Empleando información obtenida a partir de registros sanitarios electrónicos, aplicamos una variedad de métodos de ciencia de datos para la inferencia causal basada en datos observacionales. Primero, realizamos una evaluación a nivel ecológico del nivel de implementación de la intervención ARSUIC, empleando el tiempo entre el alta hospitalaria y la primera cita ambulatoria como variable resultado. Después, emulamos dos ensayos clínicos pragmáticos inviables comparando, en primer lugar, participantes que recibieron la intervención ARSUIC con una cohorte histórica en un diseño de tipo espejo y, posteriormente, participantes que recibieron ARSUIC, Contacto Aumentado y Psicoterapia, empleando un método de seguimiento y medición similar para los tres centros. Todos los estudios de nivel individual fueron ajustados para reducir sesgo de confusión, empleando modelos multivariados de riesgos proporcionales de Cox informados por información teórica que se expresó en forma de gráficos acíclicos direccionales. Finalmente, condujimos un estudio de coste-efectividad, desde la perspectiva de la sociedad, derivando análisis de sensibilidad de tipo determinista y probabilístico, para orientar la toma de decisiones en materia de gestión de recursos.

4.1 Study setting, data source, and overall methodological approach

4.1.1 Study setting and data source

In Spain, a National Health Service (NHS) funded by taxes provides universal access to medical care. The Community of Madrid's Health Council coordinates 25 healthcare catchment areas.

Each area features a General Hospital and includes a Psychiatry Department offering a range of in- and out-patient care and rehabilitation resources, to which General Practitioners and other specialists refer patients who require mental healthcare. Most of the patients with psychiatric needs use this network, and they usually come from primary care.

In addition, all catchment areas have implemented longitudinal electronic healthcare records for data collection for healthcare and administrative purposes. Even though these records are specific to each catchment area and, as a result, not all records include all variables, they feature a high number of non-selected patients, followed-up for several years. Applying adequate data science methods and under a correctly specified framework, large healthcare records are useful for several tasks within epidemiology (Hernán et al., 2019): for instance, they can be used for description (Martínez-Alés et al., 2019e; Bouza et al., 2019; López-Cuadrado et al., 2019) or for prediction (Kessler et al., 2015; Simon et al., 2018). Likewise, these large electronic healthcare records can be viewed as an opportunity to draw causal inferences with high external validity that can be readily applicable by decision-makers. Notwithstanding, data retrieved from electronic healthcare records are, by definition, observational. The following section reviews specific characteristics and assumptions of the thinking framework under which we conducted our analyses and drew our conclusions.

4.1.2 Overall methodological approach: using administrative healthcare databases for causal inference

The objective of our study implied calculating several causal effects. First, we wanted to know the causal effect of deploying a mandatory program on the distribution of time to first consultation following hospital discharge after a suicide attempt. Second, we wanted to estimate and compare the causal effects of three different strategies on the individual risk of suicide re-attempt. However, answering causal questions with observational data poses inherent challenges (Hernán and Robins, 2019). The following section examines the theoretical and methodological framework under which we conducted our causal analyses.

Mackie (1965) and Rothman (1976) defined a cause of a given outcome as a factor preceding the outcome so that, in the absence of that factor, the outcome would not have occurred, or it would have occurred at a different moment. This widely accepted definition of cause and effect implies what has been called the *fundamental problem of causal inference* (Holland, 1986): causal inference would require, in theory, the comparison of the factual, observable universe to another *counterfactual* (and hence unobservable) one where everything but the potential cause under study was held equal.

In an attempt to bypass this fundamental problem, researchers usually resort to study designs that randomly assign participants to the causal factor (treatment) under study. In short, random assignment generates treatment groups that are exchangeable, or comparable in expectation (Deaton and Cartwright, 2017), because randomization ensures that the mechanism of assignment of the causal factor under study is independent of the individual's characteristics. Observational studies, on the contrary, must deal with the possibility that characteristics of the individual may, at the same time, be associated (causally or not) with both the treatment and the outcome. This phenomenon, commonly termed *confounding*, can lead to spurious correlations between the cause and effect under study and bias the study's findings. Accordingly, several analytical methods, mostly based on multivariable regression analysis, have been developed for researchers to adjust for confounding in observational research and obtain exchangeability to some degree (Hernán and Robins, 2019). All of these methods require a correct specification of the causal structure underlying the research question of interest (Hernán et al., 2002) and, in turn, depend on how correct this model is. First introduced in philosophy and computer science (Pearl, 2009), directed acyclic graphs (DAGs) are an increasingly used approach to guide confounding adjustment in observational epidemiology and to enhance communication between scientists, by forcing the researcher to clarify the assumptions underlying their model specification and the choice of variables for adjustment control. Hernán and Robins (2019) provide a succinct tutorial on the use of DAGs for confounding control. For clarification purposes, figure 1 depicts the general DAG that we

followed to guide our multivariable adjustments for confounding. In situations where we were not sure of the most correct multivariable model according to our theoretical framework, two different models were undertaken as a means of sensitivity analysis.

An additional consideration should be made when using observational data for comparative effectiveness research or, in other words, when emulating an unfeasible target trial with non-experimental data. Even in the presence of exchangeability, extensive research has shown that observational data provide better estimates of what would be observed in a randomized trial if the intervention under study is well-defined (Hernán et al., 2008), a requirement that has also been termed the Stable Unit Treatment Value Assumption (SUTVA) (Cox, 1958). In our study, we adopt a target trial approach by specifying the interventions under study, setting time zero of our participants' follow-up when they are admitted to their treatments, adopting similar criteria for participant admission and comparable follow-up methods across treatments, and analyzing the data from an intention-to-treat perspective. In addition, we evaluate the degree of fulfillment of the interventions as a means to evaluate the validity of this intention-to-treat approach.

Last, it should be noted that causes can act at several levels of organization (the ecological, the individual, the molecular, and their variations) (Susser, 1972), and be variably distal or proximal in relation to the outcome of interest (Phelan and Link, 1995). For example, for suicide, while a high rate of gun ownership may act at the ecological level, enduring a psychiatric disorder may act at the individual one; and while having been born in a socioeconomically deprived neighbourhood may be a distal cause, an acute state of alcohol intoxication may be a proximal one. Public health practice often deals with causes that act on several levels, following complex hierarchical networks - we have examined the multilevel framework of causation in detail elsewhere (Martínez-Alés et al., 2019c). In clinical settings, however, comparative effectiveness and outcomes research is typically interested in estimating the causal effects of treatments – proximal causes that act at the individual level.

Our study considered distinct research questions that can be framed at different causation levels. In particular, our first specific aim looked at the result of deploying the ARSUIC program, a mandatory and universal intervention, on the average time between hospital discharge and the first outpatient visit following a suicide attempt, and on the proportion of patients fulfilling the objective of the intervention. While caution is required before concluding causal relations at the individual level, because of the risk of engaging in what is commonly referred to as an *ecological fallacy*, we chose an ecological unit of analysis because the unit of intervention here was supra-individual (indeed, the program was effectively deployed at the province level). Using individual-level data to inform decision-makers regarding these specific implementation outcomes would entail a similar risk of a cross-level inference bias, in this case called atomistic fallacy (Schwartz, 1994). The rest of our specific aims, on the other hand, considered cause and effect at the level of individual participants.

4.2 Methods for the specific study aims

4.2.1 Evaluation of the implementation of the ARSUIC intervention

4.2.1.1 Study design, subjects, and variables

Information regarding dates of admission and discharge was obtained from the hospital's electronic healthcare records (EHR). These records are filed as a requirement before any discharge, and they also include sociodemographic variables: gender, age and whether the suicide attempt was an index attempt or a reattempt. Information regarding the first outpatient visit following discharge, and whether the patient complied with it, was retrieved from each CMHC's EHR. To evaluate the degree of implementation, we computed the time between hospital discharge and the first CMHC outpatient visit within the first 30 days. By doing so, we prevented other visits, most likely unrelated to the suicide attempt, from biasing our estimates. This bias would have favored most recently registered cases, because their follow-up periods encompass shorter time windows.

We studied time-to-first outpatient visit as a continuous variable, as well as an implementation dichotomous variable (proportion of patients actually seen within a maximum 7 days). In addition, we computed the proportion of subjects who did not have an outpatient visit after the attempt. Using the dates of hospital admission and discharge, we were able to calculate the interval of time between attempts in those patients who had more than a suicide attempt during the study period. Then, to estimate the effectiveness of the program, we obtained the time between attempts within the first follow-up year after each attempt, and the suicide attempt rate per person-year in each of the study years.

4.2.1.2 Statistical analyses

We obtained descriptive statistics of the study population's sociodemographic variables. They were summarized as percentages in categorical variables, and as the median±standard deviation in continuous ones. Then, we calculated: time between discharge and the first outpatient visit; time between different attempts; and suicide attempt rate per person-year. We tested that continuous variables were followed a parametric distribution using Kolmogorov-Smirnov's test, we studied temporal trends using Pearson's R coefficients, and we tested before-after implementation differences using Student's t-test for repeated measures. Last, we studied time trends in suicide attempt rates per person-year by fitting a generalized linear model (GLM). Inter-annual rate logarithm comparisons were adjusted for multiple comparisons using Bonferroni's method. We conducted all analyses using SPSS v.22 for Windows (IBM Corp, 2013, Armonk, NY, USA). Graphics were programmed using Stata v. 13 for Mac (Statacorp, 2013, College Station, TX, USA).

4.2.2 Evaluation of the clinical effectiveness of the ARSUIC intervention

4.2.2.1 Study design, subjects, and variables

We conducted an observational study. Between January 1st, 2010, and December 31st, 2015, every suicide attempt receiving medical and psychiatric attention at the ED entered the study, regardless of whether admission to a medical or psychiatric ward was indicated following ED

discharge. In this particular ED, every subject in an emergency psychiatric need first undergoes general medical assessment and treatment and then receives psychiatric care. In addition, anybody presenting with suicidal ideation or a suicide attempt has to be seen by a psychiatry consultant before hospital discharge. If medical damage due to the suicide attempt requires admission in a medical ward, a psychiatrist evaluates the patient once stabilized. If the psychiatrist considers that the relapse risk remains excessively high, voluntary or involuntary psychiatric admission can be indicated. We defined suicide attempt as any self-injurious act committed with at least some intent to die as a result. Therefore, we excluded patients exhibiting suicidal ideation without suicidal behavior. Otherwise, every suicide attempt was admitted to the study and included in the analyses. We considered each attempt a unit of analysis given that the intervention was widely administered at discharge, regardless of whether it was a first suicide attempt or a relapse. The study protocol complies with the Declaration of Helsinki for Human Rights and has the approval of the La Paz General Hospital's Ethical and Clinical Research Committee. Data were anonymized before extracting sociodemographic and clinical information from patient records.

Information of prognostic interest was selected according to prior existing knowledge (Turecki & Brent, 2015; Arias et al., 2016). By protocol, an individual semi-structured interview is performed prior to hospital discharge and stored in computer databases for clinical purposes. In addition, we reviewed each subject's historical medical records to identify previous attempts and psychiatric diagnoses. Clinical variables included the following: personal history of psychiatric disorder, previous suicide attempts, concurrent alcohol or abuse drugs use and hospital admission after the attempt. Sociodemographics considered age (continuous variable), and gender and family support after discharge (dichotomous variables). Additional dichotomous variables regarding psychiatric diagnoses in medical records were included, according to the presence or absence of ICD-10, chapter V, F10-69 diagnostic groups (mental and behavioral disorders due to psychoactive substance use; schizophrenia, schizotypal and delusional disorders; mood disorders; neurotic, stress-related and somatoform disorders; behavioral

syndromes associated with physiological disturbances and physical factors; and disorders of adult personality and behavior) (World Health Organization, 1992). We defined the outcome of interest as being admitted to the emergency department due to a new suicide attempt (any self-injurious act committed with at least some intent to die) during the follow-up after a previous suicide attempt. If a recurrence happened during follow-up time, it was considered a relapse, and the time between attempts was measured. Time to the event of interest was obtained from hospital's records. Every attempt, and its follow-up time, was considered.

4.2.2.2 Statistical analyses

Suicide attempts were divided according to whether they had happened in the three years prior to the program implementation, the “control period” (2010-2012), or the three ones during the “intervention period” (2013-2015). Initially, we compared baseline clinical and sociodemographic correlates in both periods, using Student's T test for differences in continuous variables and Pearson's Chi-square test for those in categorical ones. Then, we conducted a survival analysis. We censored those subjects who had not suffered the outcome of interest by the end of each period's follow-up. We obtained Kaplan-Meier estimates of the survival function, both for the whole study time and by periods. We tested the difference between periods using Log-Rank test. In order to estimate the intervention's influence in the risk of relapse, we conducted Cox proportional hazard regressions, obtaining crude and adjusted risk estimates (Hazard Ratio, HR). For the multivariate models, we retained those covariates remaining significant to the $p < .10$ level, utilizing a non-automatic method for their introduction, as well as those variables considered to be clinically relevant according to prior knowledge. Number of relapses during the follow-up was included as a continuous variable, in order to control its possible role as a source of confounding. Then, we estimated the Number Needed to Treat (NNT) and its 95% CI from the multivariate model B, following widely accepted methods (Altman and Andersen, 1999). The fulfillment of proportional hazards assumption requirements was ascertained both through graphic methods and using Schoenfeld's test. Analyses were carried on Stata v13 software for Mac (StataCorp, 2013. College Station, TX, USA).

4.2.3 Comparative effectiveness of Enhanced Contact, Psychotherapy and ARSUIC

4.2.3.1 Study design, subjects, and variables

We conducted an observational study. We included all suicide attempters who, after discharge, had entered each center's suicide prevention program between January 1st, 2013, and December 31st, 2016, and followed them for 1 year. We considered a suicide attempt any self-injurious act committed with at least some intent to die as a result of the act. Thus, we excluded individuals with suicidal ideation but without suicidal behavior. The study protocol complies with the Declaration of Helsinki for Human Rights. Approval was obtained from the corresponding ethics committees in each catchment area. Data from patient records were anonymized before extracting sociodemographic and clinical details.

Our primary outcome was relapse after a suicide attempt. We defined it as being treated again at the reference hospital, due to another suicide attempt, after hospital discharge and during a 1-year long follow-up. Time to relapse was obtained from the hospital's records. For subjects experiencing multiple relapses, we retained only the first one after entering the study. Data on clinical and sociodemographic variables of prognostic interest was obtained from pre-discharge semi-structured interviews, regularly performed by psychiatrists and stored in computer databases for clinical purposes. We selected the following sociodemographics: age (continuous variable), gender, immigrant status and cohabitation status (binary variables). Clinical variables recorded as dichotomous included: personal history of a diagnosed psychiatric disorder, personal history of suicide attempts, concurrent alcohol or drug consumption at the moment of the attempt, presence of comorbid medical conditions and main diagnosis at discharge –encoded according to ICD-10, chapter V, F10-69 diagnostic groups (mental and behavioral disorders due to psychoactive substance use; schizophrenia, schizotypal and delusional disorders; mood disorders; neurotic, stress-related and somatoform disorders; behavioral syndromes associated with physiological disturbances and physical factors; and disorders of adult personality and behavior) (World Health Organization, 1992).

4.2.3.2 Statistical analyses

Continuous variables were reported as mean (standard deviation) and categorical variables as proportions. In order to analyze baseline differences between the intervention groups in clinical and sociodemographic variables, we used Wilcoxon signs, Pearson's Chi-square and Fisher's exact tests.

We then conducted a survival analysis. Subjects who had not relapsed within one year of follow-up were censored. We obtained Kaplan-Meier estimates of the survival function by treatment group. We tested the difference using log-rank tests. In order to control for potential confounders, we conducted Cox proportional hazard regressions and obtained crude and adjusted risk estimates (hazard ratio, HR) for the different groups. For the multivariate model, we retained those covariates remaining significant to the $p < .10$ level, utilizing a non-automatic method for their introduction, as well as those variables considered to be clinically relevant according to prior knowledge. We followed widely accepted schemes for the adjustments (Hernán and Robins, 2019). Proportional hazards assumption fulfilment was ascertained both through graphic methods and using Schoenfeld's test. Then, we obtained Number Needed to Treat (NNT) estimates for both interventions compared to TAU, using an accepted method for studies where the outcome of interest is the time to an event (Altman and Andersen, 1999).

Gender and age-group differences exist in suicide and self-harm rates, and recent research shows that the young women stratum is becoming increasingly more affected (Ajdacic-Gross et al., 2008; Rockett et al., 2016). Accordingly, we conducted gender and age group-stratified Cox proportional hazard regressions, seeking for differences between programs across subgroups. We defined three different subgroups: female and ≤ 35 y-o, female and >35 y-o; and male. In order to keep reasonable statistical power for comparisons, we did not differentiate age groups within males. Analyses were carried on Stata v13 software (StataCorp, 2013. College Station, TX, USA).

4.2.4 Comparative cost-effectiveness

4.2.4.1 Study design, subjects, and variables (See 4.2.3.1.)

4.2.4.2 Cost-effectiveness statistical analyses

4.2.4.2.1 EFFECTIVENESS

Our outcome of interest was relapse within 1 year of follow-up after hospital discharge defined as being treated again at the emergency department for a new suicide attempt using the same definition. For patients with >1 suicide attempt over the follow-up period, we retained only the first re-attempt. Time to relapse was calculated using each hospital's electronic records. Comparisons used TAU as the reference group and were adjusted using multivariable Cox regression models and expressed as hazard ratios (HR) with 95% confidence intervals (95% CI) (Martinez-Ales et al., 2019f). We derived adjusted proportions of relapses (95% CI) for Enhanced Contact and Psychotherapy by multiplying the proportion of relapses among the TAU group by the adjusted HR (95% CI) of the Enhanced Contact and the Psychotherapy groups. Then, we modeled effectiveness as (1 - the probability of suicide re-attempt) for each intervention. In addition, we obtained estimates of the head-to-head comparison between Enhanced Contact and Psychotherapy, expressed as HR (95% CI).

4.2.4.2.2 RESOURCE USE AND COSTS

We considered a societal perspective that includes the healthcare perspective (all direct medical and non-medical costs) as well as the indirect costs due to work productivity lost because of sick leave or death.

We calculated the rate of service use per intervention based on information retrieved from electronic healthcare records (EHRs) for TAU, and on the protocol for Enhanced Contact and Psychotherapy. The assumption underlying this choice is that the cost for each participant pertaining to the Enhanced Contact and Psychotherapy groups equaled the cost of TAU plus the cost of each intervention's per-protocol service use, regardless of participants' adherence. All relapses were considered to incur in a minimum cost due to emergency department visit, unless

the re-attempt had been fatal. Unfortunately, the EHRs of the areas where the three interventions were implemented were found to not contain the same information regarding key variables. Accordingly, we used EHRs from the Psychotherapy catchment area to calculate the probability of receiving extra-hospitalary care and ambulance transportation, and EHRs from the Enhanced Contact catchment area to calculate the probability of hospital admission (including admission to an intensive care unit, a medical or surgical ward, or a psychiatric ward). This decision assumes that the proportions of extra-hospitalary care and ambulance transportation and of hospital admission after emergency department visit, as well as the distribution of costs after hospital admission, were similar across study centers. Then, we imputed direct costs based on the official list of public healthcare prices and fees that the Community of Madrid uses to fund medical providers (BOCM, 2017). In this list, extra-hospitalary emergency care interventions and emergency department/outpatient visits are valued on a flat rate basis, while in-patient medical costs are calculated based on Diagnostic-Related Groups (DRGs).

These data, that represent the healthcare perspective, were combined with estimates of the indirect costs due to death and sick leave to obtain the societal perspective. Again in this case, not all EHRs contained enough information regarding the probability of death and sick leave, and we had to assume a similar distribution across centers. The probability of death per relapse was obtained from the EHRs of the Psychotherapy area, and the probability of sick leave per relapse, as well as the distribution of sick leave days, from the EHRs of the Enhanced Contact area. To consider the cost of death, we used the present value of lifetime earnings (PVLE) methodology, hence assuming a loss of productive years calculated considering Spain's current average retirement age, 65y (Instituto Nacional de Estadística, 2019) and the mean age of the deceased participants. Despite valid critiques to this methodology, we consider that it yields conservative, conceptually comprehensible estimates. Costs of death and indirect costs due to sick leaves were estimated based on Spain's average annual monthly wage over the study period (EUR 1880) (Instituto Nacional de Estadística, 2017). We did not have to impute any cost or

probability based on the literature. Given the 1 year-long follow-up, we did not include any discount or inflation in cost calculations.

4.2.4.2.3 COST-EFFECTIVENESS AND SENSITIVITY ANALYSES

We calculated incremental cost-effectiveness ratios (ICERs: incremental cost divided by the incremental effectiveness) comparing Enhanced Contact vs TAU and Psychotherapy vs TAU (see below formula 1). The expected value cost of each intervention was obtained by multiplying the rate of service use and the probabilities of each outcome (death; medical care including extra-hospitalary care, emergency visit, and admission to an intensive care unit or a medical or psychiatric ward; and sick leave) by their cost (formula 2).

We conducted a deterministic sensitivity analysis to estimate the role that potential uncertainty may have on our cost-effectiveness estimates. To that end, we considered 3 potential scenarios: base case (formula 1), most favorable (formula 3), and least favorable (formula 4) to the studied interventions, using the 95% CI upper and lower limits (UL and LL, respectively) of the effectiveness estimates, and adding and subtracting a 15% to the estimates of the costs. To calculate ICERs in the most and least favorable scenarios, respectively, we used the lowest cost estimate and the highest effectiveness estimate, and the highest cost estimate and the lowest effectiveness estimate.

$$ICER_{A vs B} = \frac{C_A - C_B}{E_A - E_B}$$

(1)

$$C_x = C_{ix} + C_D P(R|X)P(D|R) + C_A P(R|X)P(A|X) + C_{SL} P(R|X)P(SL|R)$$

(2)

Where,

C = Cost; E = Effectiveness; $x \in \{A, B\}$; ix = X Intervention; D = Death; R = Relapse; A = Admission; and SL = Sick Leave

$$ICER_{most\ favorable\ A\ vs\ B} = \frac{C-15\%_A - C-15\%_B}{E\ 95\%\ CI\ (UL)_A - E\ 95\%\ CI\ (UL)_B}$$

(3)

$$ICER_{least\ favorable\ A\ vs\ B} = \frac{C+15\%_A - C+15\%_B}{E\ 95\%\ CI\ (LL)_A - E\ 95\%\ CI\ (LL)_B}$$

(4)

Because Enhanced Contact and Psychotherapy showed identical performance regarding clinical effectiveness, we compared them conducting a cost-minimization analysis.

Finally, we conducted a probabilistic sensitivity analysis where we ran 10,000 simulations of the base case scenario varying all possible parameters at random, based on the distribution of our data, following Bernecker et al's method (2019). All analyses were conducted in Stata version 14 for PC (StataCorp, 2015), Microsoft Excel (2017), and R Studio, using ggplot2 and ggpubr packages.

5. Results

Abstract

For the ARSUIC intervention, we found that median time between discharge and the first visit decreased from 8.5 to 6 days after program deployment, with the proportion of visits within 7 days increasing from 32 to 48.5%. Compared to the prior treatment as usual, we obtained that receiving ARSUIC entailed a 24% adjusted risk reduction of the risk of suicide re-attempt. Both individual Psychotherapy and Enhanced Contact were more effective than ARSUIC, with a similar 40% lower relapse risk in adjusted models for both study treatments and resulted cost-effective with a high probability. Enhanced Contact was slightly cost saving in comparison to Psychotherapy.

Resumen

Al estudiar ARSUIC, encontramos que el tiempo mediano entre el alta y la primera visita ambulatoria se redujo de 8,5 a 6 días después de implementar el programa, y la proporción de visitas en menos de 7 días aumentó de 32 a 48,5%. En comparación con el tratamiento habitual previo, ARSUIC implicó una reducción del riesgo de reintento de suicidio del 24%. Tanto la Psicoterapia individual como el Contacto Aumentado resultaron más efectivos que ARSUIC, con una reducción del riesgo del 40% en ambos casos en modelos ajustados, y coste-efectivas con alta probabilidad. Contacto Aumentado implicó gastos ligeramente menores en comparación con Psicoterapia.

5.1 Overall study results

The ecological-level assessment of the implementation of the ARSUIC intervention showed that, after program deployment, median time between discharge and the first visit decreased from 8.5 to 6 days, and the percentage of visits that fulfill the program's objective increased from 32 to 48.5%. Between years 2012 and 2015, the suicide attempt rate per person and year decreased from 1.20 to 1.08 and the proportion of attempts corresponding to relapses from 26.6% to 12.8%. When studying the effectiveness of ARSUIC, compared to the prior treatment as usual, we obtained that subjects exposed to ARSUIC had a lower risk of relapse after a suicide attempt, with a 24% adjusted risk reduction estimate. Moreover, the comparison of ARSUIC and Enhanced Contact and Psychotherapy indicated that the psychotherapy group had a lower presence of known risk factors for suicide attempt, and that both individual Psychotherapy and Enhanced Contact were more effective at reducing suicide reattempt than a single priority

appointment, with a similar 40% lower relapse risk in adjusted models for both study treatments. Notably, these results did not differ after gender and age-stratification. Finally, we found that both Enhanced Contact and Psychotherapy were cost-effective with a high probability, considering reasonable thresholds of willingness-to-pay in accordance with the literature. In addition, given that both interventions were equally effective, Enhanced Contact was slightly cost saving in comparison to Psychotherapy.

5.2 Specific study results

5.2.1 Evaluation of the implementation of the ARSUIC intervention

During the study period, a total 886 suicide attempts fulfilling inclusion criteria received medical assistance at La Paz University Hospital. The majority of them corresponded with females (68.2%). Table 1 summarizes the demographic characteristics of the study population, divided by study year.

5.2.1.1 Time between discharge and the first outpatient visit.

Studying the distribution of the intervals of time between hospital discharge and first outpatient visit within 30 days, we found that year 2012's median±standard deviation 8.5±7.6 days were reduced, after the implementation of the program, to 6±7.3 in 2013 (p=0.03). We found an inverse correlation between study year and time between discharge and first visit, indicating a progressive increase in the program's real uptake (R= -0.11; p<0.001). Figure 2 represents this association. Table 2 displays the percentage of cases who were compliant with the program's main goal – having a consultation within 7 days, per study year. It also features the proportion of cases with no outpatient consultation. Given that a longer follow-up period increases the odds of having at least one visit after the index suicide attempt, this variable became slightly lower as the study advanced.

5.2.1.2 Proportion of suicide reattempts, attempt rate per person-year and time between attempts

The distribution of suicide attempts per year was as follows: 199 cases in 2012, 242 cases in 2013, 265 cases in 2014, and 180 cases in 2015. Figure 3 shows the evolution in the proportion of attempts that corresponds to reattempts, a figure that decreased every study year. Figure 4 represents the evolution of the attempt rate per person-year throughout the study period. The rate decreased from 1.20 attempts in 2012 to 1.08 attempts in 2015 ($p=0.01$). Figure 5 shows the distribution of the intervals of time to reattempt, within a maximum 1-year follow-up, per study year: time between attempts progressively increased as the study advanced.

5.2.2 Evaluation of the clinical effectiveness of the ARSUIC intervention

5.2.2.1 Clinical and demographic characteristics

We included data from 2,347 suicide attempts treated at the ED by a psychiatrist, between January 1st, 2010 and December 31st 2015. “Control period” comprised 1,176 attempts, while “intervention period” included 1,171. Globally, 1,775 subjects attempted suicide. Figure 6 illustrates the attempt-reattempt distribution across the study subjects. Thirty-nine subjects were excluded due to computer-related data mistakes. The two major repeaters suffered 14 suicide attempts during the time of study. Table 3 shows baseline characteristics of the included cases, both for the whole study period and by treatment groups. In most cases, the subject was female (68.3%) and the mean age in years was 40.5. As for the most relevant risk factors, 73.9% had a personal history of at least one psychiatric disorder, 40.3% had a substance abuse disorder, and 48.4% had previously attempted suicide at least once. Most frequent psychiatric diagnoses were: “Mental and behavioral disorders due to psychoactive substance use” (37.5%), “Neurotic, stress-related and somatoform disorders” (37.5%) and “Mood (affective) disorders” (39.4%). Comparing both groups showed that control period had a lower prevalence of family support (62.3% vs. 74.5%), a lower presence of concurrent alcohol/drug abuse (39.1% vs. 41.4%) and a higher percentage of inpatient admission after the suicide attempt (24.5% vs. 20.5%).

5.2.2.2 Follow-up and relapse

A total 497 (21.2%) cases relapsed during follow-up. The intervention group had a lower incidence of relapse during follow-up (18.3% vs. 24.1%; $P < .01$). Curves obtained from Kaplan-Meier survival probability and multivariate adjusted survivor functions are shown in Figure 7. Median follow up was 434 days for the whole study, 394 for the control group and 468 for the intervention group. Differences between control and intervention group's survival probability estimates are statistically significant (Log-Rank test $P < .01$). Table 4 displays results from the adjusted and unadjusted Cox proportional hazard models. Univariate models showed an association between a higher risk of relapse and the following risk factors: personal history of psychiatric disorders, personal history of suicide attempts and concurrent alcohol or drug abuse. The presence of social support was a protective factor. For the multivariate models, we retained those variables that were significant at the $p < .05$ level (multivariate model A), as well as those variables considered clinically relevant (multivariate model B). Results show that attempts followed by a scheduled priority appointment had a lower risk of relapse, with little difference between estimates from the unadjusted model, HR (95%CI) = 0.72(0.60-0.82), and the multivariate models A, HR(95%CI) = 0.76(0.62-0.93) and B, HR(95%CI) = 0.69(0.54-0.87). The proportional hazards assumption was fulfilled (Schoenfeld's Residuals test $P = .30$; $P = .15$ and $P = .14$ for the univariate and multivariate models A and B, respectively). The NNT (95% CI) estimate obtained from the multivariate model B was 7.7 (4.5-20.0).

5.2.3 Comparative effectiveness of Enhanced Contact, Psychotherapy and ARSUIC

5.2.3.1 Clinical and demographic characteristics

We included data from 1,492 patients who had attempted suicide and subsequently entered the suicide prevention program at one of the three hospitals, between January 1st, 2013 and December 31st, 2016. Table 5 summarizes baseline characteristics of the study subjects, both globally and per intervention group.

5.2.3.2 Intervention group baseline differences

Baseline covariates showed comparable inter-group age distribution, a higher percentage of females in the Enhanced Contact group, along with several differences regarding clinical and social covariables. Subjects receiving TAU (the majority of the study participants) had proportions of psychiatric history (70.3%), previous suicide attempts (34.5%) and concurrent alcohol or drug abuse (35.7%) that fall halfway to that of the other two treatment groups, suggesting that this cohort had an intermediate level of clinical severity. As for social correlates, subjects receiving TAU had the lowest levels of both immigration and household cohabitation. The sample receiving psychotherapy, formed by one third of the subjects, had the lowest prevalence of the abovementioned clinical covariables, intermediate levels of immigration and relatively high levels of cohabitation. Participants receiving enhanced contact, the smallest group, had the highest prevalence of previous psychiatric conditions, immigration, and previous suicide attempts and drug/alcohol abuse. Regarding main diagnoses at discharge, the Psychotherapy and Enhanced Contact groups had similar rates of neurotic, stress-related and somatoform disorders, and the latter also showed a high presence of disorders of adult personality and behavior, while TAU participants were more frequently diagnosed as having mood disorders. These findings, suggesting the Psychotherapy group included a less severe sample, make sense as this intervention only included subjects who did not have an ongoing outpatient therapeutic treatment.

5.2.3.3 Follow-up and relapse

A total 133 (8.9%) subjects experienced a relapse during follow-up. TAU had twice the crude incidence of the psychotherapy group, while the enhanced contact group had an intermediate figure. Mean days (95% confidence interval) of follow up were: TAU: 335.8 (329.7-341.9), Enhanced Contact: 347.4 (337.2-357.6) and Psychotherapy: 349.6 (343.8-355.3), for a global: 342.0 (338.0-346.1).

Curves obtained from Kaplan-Meier survival probability function estimates per intervention group, as well as multivariate adjusted survivor functions, are presented in figure 8. Differences between TAU and both Psychotherapy and Enhanced Contacts groups in Kaplan-Meier estimates are statistically significant (log-rank test $p=0.001$).

Table 6 displays results arising from Cox proportional hazard models, including unadjusted and adjusted estimates. Univariate regressions showed an association between a higher risk of relapse and several measured risk factors: a personal history of suicide attempts, concurrent alcohol or drug abuse and a comorbid condition. Among psychiatric conditions diagnosed, mood and personality disorders stood out as risk factors, and adjustment and stress disorders behaved as protective factors. Immigration also showed a protective effect. On the other hand, female gender did not achieve statistical significance, and neither did cohabitation or age in years. We fitted a subsequent multivariate regression, following a non-automatic method, and delivered an adjusted model. We controlled for age, gender, previous suicide attempts, alcohol or drug abuse, mood (affective) and personality disorders. The fulfilment of the proportional hazards assumption was checked: Schoenfeld's Residuals test $p=.26$ and $p=.13$ for the univariate and multivariate models, respectively. Using the adjusted regression, we estimated the NNT (95%CI) for each intervention compared to TAU, resulting on 6.7 (3.3-100.0) for Psychotherapy and 5.3 (2.6-1000.0) for Enhanced Contact. An alternative multivariate model, including the more general personal history of a psychiatric disorder instead of specific diagnoses, resulted in similar estimates and served as a sensitivity analysis (table 7).

We obtained age- and gender-stratified multivariate estimates (table 8). Although the smaller resulting sample of subjects per stratum made the confidence intervals wider, the effect estimates of both interventions were not altered across gender groups or between younger and older females. Mood (affective) and personality disorders, previous suicide attempts and concurrent alcohol or drug abuse also had comparable effect sizes with wider confidence intervals across groups.

5.2.4 Comparative cost-effectiveness

5.2.4.1 Effectiveness

For subjects who received TAU, the probability of relapse over a one-year follow-up was 11.4% (95% CI: 10.2-12.6). Table 9 summarizes the adjusted relapse rates (95% CI) for Enhanced Contact and Psychotherapy. Notably, the head-to-head comparison between Enhanced Contact and Psychotherapy showed practically identical effectiveness estimates (HR=0.99; 95% CI= 0.51-1.96).

5.2.4.2 Costs

First, we computed the direct medical cost per patient receiving each of the interventions. We estimated the basic annual cost of TAU to be EUR 311 per participant. Psychotherapy costed an estimated additional EUR 664 (total cost EUR 975 per participant), and Enhanced Contact an additional EUR 468 (total cost EUR 779 per participant).

Then, per each suicide re-attempt, we calculated a direct medical cost of EUR 190 if it only required a one-day stay at the Emergency Department, and an additional EUR 4,163 if the patient was hospitalized. Direct non-medical costs due to transportation by ambulance were EUR 280. Finally, we estimated indirect costs worth EUR 543,696 in case of death and EUR 62.6 per day of sick leave following the re-attempt. Figure 9 shows the decision-analytic model of distribution of costs. Based on information retrieved from EHRs, we weighted each of these costs by the probability of each potential outcome per suicide re-attempt.

Table 10 includes information on how we computed the base case scenario costs for each intervention and of each suicide re-attempt, including the source of each datum, as well as when considering the less and most favorable scenarios for the deterministic sensitivity analysis, and the distribution parameters used for simulations in the probabilistic sensitivity analysis.

5.2.4.3 Cost-effectiveness

Table 11 shows the ICER estimates of each of the possible comparisons under the three proposed scenarios. Under the base case scenario, Enhanced Contact entailed an ICER of EUR 2,340 per averted attempt compared to TAU, a figure that rose to EUR 6,260 for Psychotherapy. As Enhanced Contact and Psychotherapy were similarly effective, a cost-minimization assessment indicated that the former was slightly cost saving compared to the latter (base case scenario: EUR -196, best case scenario: EUR -167, and worst case scenario: EUR -225 per participant).

5.2.4.4 Sensitivity analysis

Under the most favorable case scenario of the deterministic sensitivity analysis, Enhanced Contact was dominant, and Psychotherapy remained more costly when compared to TAU (EUR -27 and 489 per averted attempt, respectively) (table 11). Under the least favorable scenario, both interventions under study were markedly more costly than TAU (EUR 30,356 and 20,186 per averted attempt, respectively) (table 11). Figure 10 displays the distribution of the simulations obtained as a result of the probabilistic sensitivity analysis.

6. Discussion

Abstract

This is the first study to evaluate three strategies for suicide prevention at the individual level currently deployed in the Community of Madrid. The implementation ARSUIC intervention, a priority appointment scheduled before hospital discharge, had a reasonable uptake, effectively reducing the average time between discharge and the first outpatient visit among participants. Moreover, ARSUIC was effective at lowering the risk of relapse among suicide attempters, reducing re-attempts by 24%. The two augmentation strategies under study, Enhanced Contact and Psychotherapy, posed a similar, additional benefit to that of ARSUIC, lowering the risk an additional 40%. In addition, both interventions were cost-effective compared to ARSUIC under acceptable thresholds of willingness to pay, and Enhanced Contact was slightly cost saving compared to Psychotherapy. Our results, based on data retrieved from the real clinical practice, should provide decision-makers with readily applicable estimates for treatment and healthcare planning purposes.

Resumen

Este es el primer estudio que evalúa las estrategias para la prevención del suicidio a nivel individual que actualmente están en uso en la Comunidad de Madrid. La implementación de la intervención ARSUIC, una cita prioritaria establecida antes del alta hospitalaria, tuvo una recepción razonable, reduciendo efectivamente el tiempo medio entre alta hospitalaria y primera cita ambulatoria. Además, ARSUIC fue efectivo reduciendo el riesgo de recaída entre personas que habían intentado el suicidio, reduciendo los reintentos un 24%. Las dos estrategias de potenciación estudiadas, Contacto Aumentado y Psicoterapia, tuvieron un similar beneficio adicional al de ARSUIC, reduciendo el riesgo un 40% añadido. Las dos intervenciones resultaron coste-efectivas, en comparación con ARSUIC, considerando límites de disposición a pagar aceptables, y Contacto Aumentado fue levemente menos costoso que Psicoterapia. Nuestros resultados, basados en datos de la práctica clínica real, deberían proveer a los decisores con estimadores directamente aplicables en términos de tratamiento y planificación sanitaria.

6.1 Overall study discussion

Ours is the first study to analyze the implementation, effectiveness and cost-effectiveness of three individual-level suicide prevention strategies currently deployed in the Community of Madrid. These results contribute to the literature on interventions to lower suicide risk among high-risk individuals by providing readily applicable estimates completely based on a naturalistic study analyzed using a variety of methods for causal inference from observational

data. Accordingly, these estimates should prove useful for decision making at several levels, including the clinical practice and healthcare planning.

The results to our first aim indicate that implementing the ARSUIC Program lowered the time between discharge and the first outpatient visit following a suicide attempt. In addition, the proportion of suicide attempts due to relapses and the suicide attempt rate per person decreased progressively. The program fulfilment proportion was under 50%, suggesting between-user differences regarding their effective access to the program. Building on those results, the evaluation of the program's clinical effectiveness suggests that an additional early appointment, scheduled before discharging suicide attempters, reduced suicide reattempt risk. Further, the comparison between ARSUIC, Enhanced Contact and Psychotherapy shows that, in a naturalistic clinical setting, patients exposed to individual psychotherapy or an enhanced contact intervention had a similar, lower relapse risk than the single priority appointment group. Finally, both programs proved cost-effective under reasonable thresholds of willingness to pay, and it seems that Enhanced Contact may be considered the treatment of choice for a general population of suicide attempters.

6.2 Specific study discussions

6.2.1 Evaluation of the implementation of the ARSUIC intervention

This retrospective study analyzed the degree of implementation and fulfillment of the ARSUIC Suicide Risk Care Program, as well as its effectiveness. Our results show that, after ARSUIC was implanted, the median time wait between a suicide attempt and the first outpatient follow-up was reduced from 8.5 to 6 days, and then it stabilized in 7 days – the exact maximum that the program allows for. Moreover, the proportion of suicide attempts seen at the ED that correspond to reattempts decreased, and time between attempts in patients with multiple attempts increased. This is the first study to evaluate this program, adopted in all hospitals across the Autonomous Community of Madrid since 2013.

Since the establishment of the program, a number of voices have rightfully pointed out the need for an evaluation of its results (Asociación Madrileña de Salud Mental, 2012). In fact, implementing suicide prevention programs that are innovative and effective, and evaluating such programs with observational designs in real-world settings, are two global priorities (Brown and Green, 2014). According to our results, median time to follow-up, considering only the first 30 days after discharge, has decreased until becoming compliant with the study's objectives. In addition, our study shows high adherence to follow-ups after suicide attempting – over 88% patients were seen at a CMHC at some point, following discharge. Notwithstanding, there is a marked proportion of patients who do not turn up to these outpatient visits within the maximum 7 days established in the program. During the study period, this proportion has lowered from 68% to roughly 50%. The figure is in keeping with a study from Barcelona, where up to 50% did not comply with a suicide risk reduction protocol based on telephone calls (Cebriá et al., 2013). Hence, while central tendency indicators suggest that ARSUIC's goals have been fulfilled, there seem to exist substantial between-subject differences in effective access to care. The marked increase of absolute suicide attempts we observed between 2012 and 2014 is in line with trends reported elsewhere (Ting et al., 2012). Our ecological assessment of the program's effectiveness is promising: the proportion of attempts corresponding to reattempts and the suicide attempt rate per person-year have decreased every year since the program was implemented.

Our study includes several limitations that may somewhat affect its validity, and the applicability of our results. First, a proportion of all patients seen at the ED was under long-term treatment in a different catchment area, indicating the possibility that some suicide attempts pertaining to our studied area were, in turn, seen at other EDs, and are not included among our study population. Other authors, from comparable healthcare settings (Parra-Uribe et al., 2017), maintain that, in Spain, most attempts are derived to the correspondent catchment area's ED. Overall, Madrid's healthcare planning has not suffered major changes during the study period, and we consider unlikely the possibility that this limitation affects between-study

year differences. Thus, we believe that our findings are valid. Second, due to technical and ethical limitations, our effectiveness assessment is based on suicide reattempt, rather than death by suicide, as the measure of effect. Most authors agree that suicide attempt, as a relatively frequent event that can be registered in the clinical setting, is a useful proxy for death by suicide, an infrequent and difficult-to-detect outcome (Harris et al., 1997; Finkelstein et al., 2015; Tejedor et al., 1999). Notwithstanding, other studies have reported profile differences between people who attempt suicide and those who die by suicide (Parra-Urbe et al., 2013), and we consider that including suicide as an outcome should be a priority in future assessments of the program. Last, our study uses an ecological and historical design to evaluate the program's effectiveness, two characteristics that limit our ability to draw causal inferences. The retrospective design increases the possibility of a potential undetected historical artifact affecting our results. For example, some authors have reported an association between the 2000s decade's economic downturn and suicide rates in Europe (López Bernal et al., 2013). The ecological approach somewhat limits our study's applicability to the clinical practice, in terms of individual-level decision-making.

Our study's main strength is its naturalistic character that allows for the assessment of a recently implemented intervention in unselected patients. There is a growing demand for pragmatic intervention studies for comparative effectiveness research that favor the generation of external rather than internal validity and expedite the implementation of evidence-based programs (Sherman et al., 2016). The age and gender distribution of our study population are in line with those observed in comparable settings (Cebriá et al., 2013). We believe that our implementation estimates can be generalized to the rest of the Autonomous Community of Madrid, and that the effectiveness estimates are valid for other universal coverage healthcare systems. In addition, evidence suggests that, just as other subpopulations of patients under mental healthcare, people who attempt suicide have lower rates of adherence to outpatient care, as well as other inequities in access to care, than the general population (Miller et al., 2017; Larkin et al., 2010). Hence, hospital contexts such as the ED are an opportunity to enhance their access to effective

interventions. Our study contributes with novel information to the field of hospital-initiated interventions for suicide prevention in high-risk individuals. Last, the ecological approach to estimating the program's effectiveness makes our results especially useful for decision-making at the healthcare policy and management level. Although most clinical studies opt for an individual-level approach, it should be noted that suicide is, by definition, a complex problem that requires the assessment of ecological-level factors and how these interact with individual-level ones (Hawton and Pirkis, 2017).

Further research is needed for a deeper understanding of the ARSUIC Suicide Risk Care Program. Clarification of the barriers and facilitators that suicidal individuals face in the process of accessing the program is a priority, in order to reduce access inequality. Also, building on other authors' findings that similar, early contact enhancement programs might not be effective in the long-run (Cebriá et al., 2015), future repetitions of this evaluation will be required. Last, Lopez-Castroman and colleagues have pointed out that most suicides take place in low and middle income countries, while research is mainly conducted in high income countries (2015b). Direct comparisons to programs deployed in the same and other contexts will allow for the identification of common components, to estimate if the program is adaptable and scalable (López-Castroman et al., 2015a).

6.2.2 Evaluation of the clinical effectiveness of the ARSUIC intervention

In this observational study, scheduling a priority outpatient psychiatry appointment lowered the risk of relapse among suicide attempters by up to 25% over a three-year follow-up. This is the first study to confirm the effectiveness of the ARSUIC Suicide Risk Attention Program, a contact enhancement intervention, currently in use throughout the Community of Madrid, Spain. Because we stuck to a strictly naturalistic design and included data from the real clinical practice, recruiting all suicide attempt patients treated at the ED level with no exclusion criteria, the results likely capture the implemented program's true effectiveness. The effect estimates are consistent with those of other interventions aimed at contact maintenance (Zalsman et al.,

2016), including studies conducted in other European countries (Reijas et al., 2013; Cebriá et al., 2013), the US (Miller, 2017) and several low and middle-income countries (Riblet, 2017). In keeping with the literature, risk factors for re-attempts included a personal history of previous suicide attempts, the presence of a diagnosed psychiatric disorder, female gender and concurrent alcohol or drug abuse, while family support was a protective factor.

Emergencies because of attempted suicide have steadily increased throughout the last decades worldwide (Zalsman et al., 2016; Ting, 2012), and their frequency typically peaks amongst the younger age groups (Canner et al., 2018). Our results contribute with relevant information regarding the effectiveness of ED-initiated outpatient preventive programs directed towards attempters, considered exceptionally high-risk individuals. Given that discharge after a suicide attempt entails a remarkably high risk of relapse, a majority of prevention strategies have focused in this period (Meerwijk et al., 2016; Milner et al., 2015). Contact-enhancing programs, specifically directed at establishing brief contacts and maximizing access to clinical and social resources, are considered effective: accordingly, a range of evidence-based contact maintenance programs including the use of letters, telephone calls, messages or case management have been successfully developed, deployed and scaled-up (Vaiva et al., 2011; Berrouguet et al., 2014; Dekker et al., 2017). Recently, the WHO Brief Intervention and Contact (WHO BIC), a strategy searching to enhance contact after a suicide attempt, was the only intervention to significantly lower the risk of suicide in a recent meta-analysis of randomized control trials (RCT) including other therapeutic and pharmacologic strategies and a variety of different locales (Riblet et al., 2017). In the ED-Safe study, an RCT conducted in North American subjects, a brief ED-based intervention, consisting on post-discharge resources and telephone calls, significantly decreased re-attempts, with an incidence rate ratio (95% CI) of 0.72 (0.52-1.00) (Miller et al., 2017). However, studying suicide behaviors using experimental designs can be technically and ethically challenging, and a call has been made to conduct effectiveness and implementation studies on naturalistic settings, in order to obtain externally-valid real-world data that can inform decision-makers (Sherman et al., 2016). Along these lines, an observational study

conducted among suicidal ED patients from Veterans Health Administration hospitals found that a brief structured intervention, including an outpatient appointment and telephone calls, increased engagement and reduced suicidal behaviors after discharge (Stanley et al., 2018). Building on the tradition of suicide prevention among high-risk individuals, our study contributes with data from the clinical practice suggesting that contact maintenance, by scheduling a single priority appointment before discharging suicide attempters from the ED, can lower the risk of suicide attempt relapse.

Suicide, a global public health concern, is the second cause of death among the Spanish youth (Instituto Nacional de Estadística, 2017). In the US, it is the only one, among the 10 leading causes of death, with an increasing rate over the last decade (Swanson et al., 2015). Suicide attempts are considered the most accurate markers for completed suicide: attempters from a multicenter controlled study in England had a 43 times higher risk of suicide (Hawton et al., 2015). However, suicide attempts demand further attention beyond their predicting role. Not only they are an opportunity for prevention but also a frequent clinical entity by themselves (for example, around 10% of Spanish citizens have attempted suicide at least once) (Gabilondo et al., 2007), with an important associated burden of economic and emotional costs and a tendency to relapse. In fact, the presence of previous suicide attempts stood out as the major risk factor, with a HR of 2.32 in our adjusted models. In our study, more than 1 out of 5 attempts subsequently relapsed, and most reattempts took place during the first months of follow-up. This figure is consistent with that of a prospective study conducted in 150 Spanish subjects after hospital discharge (Tejedor et al., 1999), while a Danish cohort including 3,690 attempts exhibited an even higher risk, around 28% (Christiansen et al., 2007).

As an addition, our study offers updated information on several clinical and socio-demographical risk factors for suicide and suicide attempts. As previously published in studies from a variety of international locations, female gender, previously diagnosed psychiatric disorders and drug or alcohol abuse carried higher risk (Holmstrand et al., 2015; Christiansen et al., 2007; Beghi et al., 2013). A recent cohort study, conducted in Barcelona, Spain, found an

increased risk in younger groups (Parra-Urbe et al., 2017), a finding that was absent in our study. However, differences could be explained because we considered age in years a continuous variable, whereas the aforementioned study used age groups, established >60 years-old as the reference group and found an almost constant risk increase across the rest of age groups.

Our main strength is an easy-to-implement, well-defined intervention – an outpatient appointment with a psychiatrist within 7 days after the ED discharge –. In the studied catchment area, ordinary consultations with specialists usually have waiting times over 19 days (Comunidad Autónoma de Madrid, 2017). We have found that median time to the first consultation after a hospital discharge, after a suicide attempt, decreased to 7 days after ARSUIC program was implemented, over 50% of the subjects were seen in the desired time window, and compliance with the program is above 88% (Jiménez-Sola et al., 2019). Previous authors have emphasized the necessity to focus on suicide prevention at the ED, where most of the highest risk patients seek help, including those with a low adherence to conventional outpatient treatment (Larkin & Beautrais, 2010). In order to evaluate the program from a pragmatic point of view, we did not exclude any of the 2,347 suicide attempts treated during the study period, regardless of clinical profiles or inpatient admissions. As a consequence, our real-world results, obtained from a naturalistic setting, may provide critical evidence for decision makers. The effect estimates remained almost unchanged across the different univariate and multivariate models, suggesting an elevated robustness. The studied location, a catchment area with universal health coverage, combines different city districts and rural areas, including a wide range of ages, nationalities and socio-economical contexts (Hortas and Onrubia, 2017). In addition to the mentioned coincidence with previous results from other places and health systems, the heterogeneity of patient profiles and social contexts included provides grounds for our results to be considered widely generalizable, especially to settings with universal medical coverage.

Our study includes several limitations. First, we lack information regarding completed suicide among the study participants. As we have mentioned, suicide attempt and death by suicide are closely associated (Olfson et al., 2017b). Suicide is a less frequent phenomenon and using re-attempt as the main outcome allowed us to detect differences between groups. Nevertheless, certain authors have found differences between the profiles of suicide attempters and achievers (Parra-Urbe et al., 2013). Hence, further research should be conducted to ascertain to which level this program also reduces suicide risk. Secondly, it is possible that certain subjects relapsed and were evaluated at a different hospital during follow-up. However, we consider this possibility unlikely: as previously published, in our setting, treated suicide attempts are systematically referred to the catchment area's General Hospital ED (Parra-Urbe et al., 2017). In addition, Madrid has high residential stability: for example, during 2017, only 2.88% of the studied area's population moved to a different catchment area (Ayuntamiento de Madrid, 2018). Besides, even though our reduced sensitivity to deaths and relapses evaluated elsewhere could lead to an underestimation of the incidence of relapse, this limitation would equally affect both treatment phases and thus not imply systematic error at the comparison level. Finally, the observational nature of our study makes it vulnerable to unascertained sources of bias. In particular, because we used a historical control group, we cannot rule out a potential sentinel or historical artifact. Notwithstanding, we consider this possibility unlikely because there is no evidence of a contemporary decrease of suicidal behaviors either in Madrid or elsewhere in Spain. On the contrary, data from outpatient and inpatient facilities suggest a general increase in such behaviors, in line with what has been observed in several samples from the US (Olfson et al., 2017a; Wester et al., 2017). A study conducted in Andalusia, Spain, analyzed data on suicide attempts using telephone call records from the public emergency healthcare system: they found that the number and rate of attempts increased annually between 2010 and 2013, the last year of study (Mejías-Martín et al., 2017). Furthermore, data from nationwide electronic registries indicate that the number of hospital discharges including any form of suicide attempt as a diagnosis also increased annually, both in Madrid (1,747 registries in 2010 and 2,418 in

2015) and in Spain (11,476 registries in 2010 and 15.857 in 2015) (Ministerio de Sanidad, Consumo y Bienestar Social, 2018).

Further studies should include evaluations considering a longer follow-up, as previous research has called into question the long-term effectiveness of brief contact programs (Cebriá et al., 2015). Head-to-head comparisons with more complex interventions implemented in other catchment areas of the same location will help clarify the differential suicide risk reduction potential of their respective components (López-Castroman et al., 2015a). Implementation studies in different locations, especially from low and middle-income countries, will define our findings' implications for Global Mental Health. As López-Castroman et al. have pointed out, most of completed suicides take place in low and middle-income, while most suicide prevention research is conducted elsewhere (2015b). In addition, comparison studies across countries can yield findings concerning supra-individual determinants of interest (Susser and Martínez-Alés, 2018). For example, recent ecological studies suggest that the late 2000s financial recession had an increased impact on suicides in Spain (Fernández-Navarro et al., 2016) and that the substantial variation in national suicide rates can be partially explained by ecological variables (Schomerus et al., 2015). Suicide is, by definition, a “complex problem” that requires a careful assessment of the interactions between risk factors and multi-level preventive interventions (Hawton and Pirkis, 2017; Hegerl and Kohl, 2016).

6.2.3 Comparative effectiveness of Enhanced Contact, Psychotherapy and ARSUIC

In this observational study, two programs, consisting of a 2-month long weekly problem-solving psychotherapy intervention followed by scheduled telephone calls (Psychotherapy) and on an early appointment followed by a 6 to 12-month long schedule of in-person visits and telephone calls (Enhanced Contact) could lower the risk of relapse after an attempted suicide by 38 and 44% during a 1-year follow-up, respectively, compared to a single priority outpatient psychiatry appointment within 7 days (TAU). The NNT estimates were 6.7 (Psychotherapy) and 5.3 (Enhanced Contact). Building on the tradition of natural experiments including real-world

clinical settings (Sherman et al., 2016), our study contributes to the identified need of head-to-head comparative effectiveness studies between detailed suicide prevention programs, in order to develop a means for a better understanding of the underlying mechanisms of different interventions (Milner et al., 2015).

The period following discharge after a suicide attempt is a time of extremely high relapse risk (Turecki and Brent, 2016). In this cohort, 8.9% of the subjects relapsed during a 12-month follow-up, a somewhat lower figure than reported during longer follow-ups in comparable settings (Tejedor et al., 1999). This is probably because contact maintenance with suicide attempters can reduce repetition of suicidal behaviors (Milner et al., 2015). Our control intervention, an early follow-up after self-harm, has shown effectiveness reducing recurrence both in our setting (Martínez-Alés et al., 2019) and in others (Inagaki et al., 2015). Also, we did not include subsequent relapses, hence excluding attempts conducted by heavy repeaters.

In keeping with the literature (Vaiva et al., 2006; Exbrayat et al., 2017), our results suggest that repeated scheduled telephone calls lower postdischarge relapse risk. Some psychotherapeutic approaches have proved useful in lowering suicide risk among certain subtypes of patients (Brown et al., 2005; Linehan et al., 2015). However, in our study, the group receiving individual problem-solving psychotherapy did not significantly differ from those only receiving intensive contact maintenance. This is unsurprising: RCTs and systematic reviews have found no benefits in adding psychotherapy to conventional treatments for unselected suicidal subjects (Goodman et al., 2016; Crawford et al., 2007).

Our study has limitations we would be remiss not to report. In order to have enough power to detect differences between groups, we chose suicide re-attempt as our outcome of interest and did not include information concerning death by suicide, an important but infrequent event. As we have mentioned, there is a close association between suicide attempt and death by suicide (Olfson et al., 2017a; Hawton and Pirkis, 2017). For example, Finkelstein et al. reported that first-time self-poisoning survivors had a completed suicide HR of 41.96 when compared to

controls (2015). Nonetheless, differences between suicide attempters and completers have been reported elsewhere (Parra-Uribe et al., 2013). Thus, we can only focus on the programs' protective role against attempted suicide. As a real-world study, we did not randomly assign the interventions. Instead, each center has different criteria for inclusion. As a matter of fact, baseline characteristics show differences across groups. Accordingly, we fitted two different multivariate models and obtained similar estimates across models, suggesting robust results. Nevertheless, we cannot rule out residual confounding or selection bias due to unmeasured correlates such as lethality, suicide attempt method or family history of suicide, and therefore the effect estimates should be carefully considered. A comparison with historical controls from each catchment area might provide useful additional effect estimates. Also, there is a possibility that certain relapses were evaluated at a different hospital during follow-up. In our context, this possibility is unlikely. First, as other authors from comparable areas of the same healthcare system have previously published, treated suicide attempts are systematically referred to the subject's catchment area's General Hospital (Parra-Uribe et al., 2017). Second, Madrid's population shows high residential stability through time: using official data from 2017, only 3.49% of the people living in one of the three studied catchment areas moved to a different district (Ayuntamiento de Madrid, 2018). All in all, this possibility does not differentially affect our studied catchment areas; thus, we consider our comparative effectiveness estimates internally valid. Lastly, it has been suggested that, just as in most complex phenomena, risk factors for suicide and suicide behaviors not only act at the individual level, but also at overarching ecological levels (Hawton and Pirkis, 2017; López-Castroman et al., 2015b). For example, the frequency of suicide ideation and attempts show remarkable differences across countries (López-Castroman et al., 2015b). However, the three intervention groups are contemporary and belong to comparable catchment areas of the same city, so we consider differences in such factors unlikely.

The strictly naturalistic enrolment of the study yields results that can be considered directly applicable. Most clinical guidelines prioritize evidence arising from RCTs. However, although

strict inclusion criteria, randomization and close follow-up provide highly internally valid efficacy estimates, their ability to also produce clinically-generalizable effectiveness estimates has been called into question.²⁷ In line with this, effectiveness estimates from clinical settings are progressively becoming a valuable source, sought after by decision-makers (Mahajan, 2015). This “real-world” approach most likely captures an intervention’s actual impact in the management of most psychiatric conditions, deeply shaped by interactions with the environment (such as suicide risk or schizophrenia) (Tiihonen et al., 2017). As previously mentioned, the results are in line with most published research on suicide attempters, both regarding the sample’s characteristics (a mean age of around 40 years, a higher percentage of females, frequent co-occurrence of alcohol or drug consumption and main diagnoses of mood, adjustment and personality disorders) (Parra-Urbe et al., 2017; Zalsman et al., 2016; Bagge et al., 2017) and the effect estimates of the implemented measures. Hence, we consider these estimates as widely generalizable, especially to contexts where, as in ours, a catchment area-based public system provides universal coverage to the population. Besides, patients were enrolled right before discharge from the General Hospital, mostly at the Emergency Department. Our study therefore supports recent studies’ claim for a focus towards suicide prevention at such settings, because of the concentration of subjects with high suicide risk and low adherence to outpatient resources (Olfson et al., 2014).

Suicide behaviors are a growing, critical public health issue: in the US, 1.1 million persons attempt suicide every year (Hogan, 2016). Even though several preventive strategies have proved useful at lowering such behaviors, selecting and promoting measures that entail an additional staff burden requires both political will and adequate evidence. Because RCTs of suicide attempt prevention interventions often have ethical limitations (Courtet, 2017), pragmatic designs using real-world data offer an advantageous approach. Nonetheless, the question if psychotherapy adds value to contact maintenance for suicidal behavior prevention remains partially unanswered.

6.2.4 Comparative cost-effectiveness

This is the first study to compare the real-world cost-effectiveness of a priority appointment, a brief contact intervention, and an individual psychotherapy program for post-discharge suicide risk prevention following an attempted suicide. Compared to a single emergency department-appointed priority visit within one week after hospital discharge (TAU), the two interventions under study (an Enhanced Contact schedule based on an increased frequency of visits and additional telephone calls and a 2-month long weekly problem-solving Psychotherapy intervention) were similarly effective at lowering the risk of suicide re-attempt over a one-year follow-up. Even though there are no official recommendations regarding willingness-to-pay per averted suicide in the literature (Park et al., 2018; Bernecker et al., 2019), both Enhanced Contact and Psychotherapy incurred incremental costs per suicide attempt averted that fall below what other researchers have considered acceptable thresholds, under any of the pre-specified scenarios (Park et al., 2018; Bernecker et al., 2019). Given that economic assessments of suicide prevention strategies are still scarce in the literature (Bustamante-Madsen, 2018), our results should provide decision-makers with key information for resource prioritization purposes.

Because the time period immediately following hospital discharge of suicide attempters entails a markedly high risk of suicidal behaviors (Turecki & Brent, 2016) and death by suicide (Olfson et al., 2017a), it provides a critical window of opportunity for prevention efforts. Accordingly, several psychosocial interventions have been specifically developed for post-discharge suicide prevention with overall comparable effectiveness rates associated to contact maintenance and psychotherapy (Riulet et al., 2017). Along those lines, we found that both Enhanced Contact and Psychotherapy were similarly effective for secondary prevention purposes. Compared to TAU, Enhanced Contact was dominant under the most favorable scenario (EUR -27 per averted attempt) and incurred in additional costs under the case-base and less favorable scenarios (EUR 2,340 and 30,356 per averted attempt, respectively), and Psychotherapy entailed additional incremental costs under all three scenarios (EUR 3,450;

6,260; and 20,186, respectively). These results do not lend themselves to easy interpretation, given the lack of consensus regarding the willingness-to-pay per averted suicide. Park and colleagues, in a recent study based on a randomized controlled trial (2018), used a willingness to pay level of CHF 30,000 (approximately EUR 28,000) to evaluate the cost-effectiveness of a contact intervention based on a combination of in-person visits and personalized letters (the ASSIP intervention). Another study evaluated the cost-effectiveness of a brief cognitive behavioral therapy intervention for suicidal US Army soldiers, finding an ICER per averted suicide ranging between USD 40,650-44,530 (approximately EUR 36,556-40,045) under the worst-case scenario (Bernecker et al., 2019). Extrapolating those figures to our study, it would be safe to conclude that both Enhanced Contact and Psychotherapy have a high probability of being cost-effective. In addition, given that both augmentation strategies had identical effectiveness (HR=0.99; 95% CI= 0.51-1.96), Enhanced Contact resulted slightly more advantageous than Psychotherapy in terms of cost minimization.

Notably, Park et al. (2018) found ASSIP to be cost saving, mainly through a shift towards less costly outpatient treatment in their participants' pattern of resource use, a result somewhat different than ours (at least under the base-case and less favorable scenarios). Three characteristics of our study design may help explain this discrepancy. First, our control group received the ARSUIC intervention, an emergency department-scheduled outpatient follow-up visit within the first week following hospital discharge. Unlike their control intervention, a single suicide risk assessment, ARSUIC has been found to be effective at lowering the risk of subsequent suicide attempting by previous research (Martínez-Alés et al., 2019f). Second, we only recorded each participant's first relapse over a 12-month follow-up, while Park et al. included all subsequent suicide attempts, including those carried out by heavy attempters. Third, our models only considered costs that could be directly attributed to the first re-attempt, while they computed all medical costs incurred during the follow-up period. These characteristics probably limited our ability to detect differences between the study groups: compared to Park

et al.'s study, we estimated a lower relapse rate among controls (11.4 per 100 participants) and a more modest mean of costs incurred over the follow-up (EUR 7,020 per relapse).

Our cost estimates are in line with previous research: a retrospective analysis conducted by Tsiachristas and colleagues based on data collected in 2014 in the United Kingdom estimated an overall mean direct medical cost per suicide attempt of GBP 809 (approximately EUR 1,056 in CPI-adjusted 2017 currency) (2017) and a report commissioned in 2005 by the government of New Zealand calculated a loss of NZD 6,350 per attempted suicide in indirect costs (approximately EUR 5,699 in CPI-adjusted 2017 currency) (O'Dea et al., 2005). Taken together with the fact that our data comes from an unselected population from the real clinical practice, this suggests that our results can be viewed as conservative cost-effectiveness estimates of high external validity that are readily applicable for decision makers from comparable healthcare systems (Sherman et al., 2016).

Our study is subject to several limitations. First, our comparative effectiveness estimates were derived from an observational study conducted in three real clinical settings. Although we adjusted all models by baseline confounders, it is possible that some residual confounding remained uncontrolled due to unmeasured variables. However, substantial bias due to residual confounding is unlikely, as our data comes from three highly comparable catchment areas of the same city, and the original effectiveness study included sensitivity analyses suggesting robust estimates (Martínez-Alés et al., 2019). Second, our study only detected suicide re-attempts at the emergency department level. It seems eminently plausible that we failed to capture a proportion of relapses not receiving hospital treatment and, more importantly, deaths by suicide occurring outside of the hospital. As a result, we probably underestimated the actual amount of costs per re-attempt. Of note, we have no reason to believe that this limitation varied by intervention, as we used a similar method for follow-up and detection across all centers. Hence, this limitation probably biased our results towards the null hypothesis, further reducing between-group differences. Third, we did not include data on the costs of training providers who deliver the interventions under study. Given that only the psychotherapeutic program

would plausibly entail additional, specific costs associated to training, it seems likely that including such data in our calculations would have yielded results differentially more positive for Enhanced Contact. Lastly, not all EHRs contained the full information regarding the probability of extra-hospitalary care, hospital admission, death and sick leave. As a result, we had to adopt the untestable assumption that all potential outcomes distribute similarly across all study centers.

In conclusion, our study suggests that two post-discharge prevention strategies (an augmented contact intervention and an individual psychotherapy program) performed similarly, both outperforming treatment as usual, with high probability, in terms of cost-effectiveness; and that augmenting contacts between individuals and providers may prove slightly more advantageous, in terms of cost minimization, than providing individualized psychotherapy. These results contribute to expand the scarce knowledge regarding the cost-effectiveness of secondary prevention strategies for suicide attempters by providing the first comparative cost-effectiveness estimates based on a head to head comparison between psychotherapy and contact maintenance.

Future steps should include studying the economic impact of applying psychotherapeutic interventions to specific subsamples of the population, given that recent research has highlighted important phenotypic variation across suicidal patients – suggesting two different patterns: stress-responsive and non-stress-responsive suicide attempters (Bernanke et al., 2017). It seems plausible that the latter subgroup, whose attempts are often planned over longer time spans and usually in the context of a major depressive disorder, may benefit more from a psychotherapeutic approach than the former, more impulsive subgroup. Also, further research is warranted in order to explore the transportability of our results to different settings and additional sources of indirect costs (such as other family members' loss of productivity) should be computed to better understand the societal costs of suicide attempts and deaths by suicide.

7. Conclusions

1. The period of time immediately following a suicide attempt implies a high risk of re-attempt. Evaluating individual-level prevention strategies specifically designed for this period, in terms of real-world implementation, effectiveness, and cost-effectiveness is a priority to guide decision-making.
2. The Autonomous Community of Madrid has introduced the Suicide Risk Attention Program (ARSUIC is its Spanish acronym), whose main intervention is a priority appointment following discharge after every suicide attempt to enhance adherence to outpatient mental healthcare.
3. Implementing ARSUIC lowered the median time between discharge and the first outpatient visit from 8.5 to 6 days, indicating a substantial uptake of the intervention in the real world.
4. The proportion of suicide attempters with no outpatient visit within 7 days decreased from 68% to 50% after program deployment. Despite the substantial uptake of the program, half of the patients did not attend the priority appointment within the target time frame.
5. Following program implementation in 2012, both the rate of suicide attempt per person and year, and the proportion of attempts corresponding to re-attempts were reduced progressively over the following years.
6. Compared to the prior treatment as usual, individuals receiving the ARSUIC intervention had a 24% lower risk of suicide re-attempt over a three-year follow-up. These results suggest that the intervention was effective at lowering relapse risk after a suicide attempt.
7. Two catchment áreas of the Community of Madrid deployed additional augmentation strategies based on enhancing ARSUIC with additional telephone and in-person contacts or with psychotherapy.
8. Augmentation strategies Enhanced Contact and Psychotherapy entailed a 40% additional reduction of suicide risk over a one-year follow-up. The difference in effectiveness between the two augmentation strategies was practically undetectable.

9. Compared to ARSUIC, both Enhanced Contact and Psychotherapy incurred additional costs that fall within reasonable thresholds of willingness to pay per suicide attempt averted.
10. Given that Enhanced Contact incurred lower costs and similar effectiveness, it resulted slightly cost minimizing in comparison to Psychotherapy.
11. As a general approach to non-selected suicide attempters, increasing the rate of contact with mental healthcare providers is, probably, the most cost-effective augmentation strategy.
12. To guide the decision of which intervention is more adequate to each patient, future research should identify individual-level predictors of a good clinical response to each treatment and study the economic impact of indicating psychotherapy for selected patients.

7. Conclusiones

1. El periodo de tiempo que sigue inmediatamente a un intento de suicidio implica un riesgo muy elevado de reintento. Evaluar las estrategias de prevención individual diseñadas específicamente para ese periodo en términos de implementación, efectividad y coste-efectividad en el mundo real es prioritario para guiar la toma de decisiones.
2. La Comunidad Autónoma de Madrid ha introducido de manera generalizada un Programa de Atención al Riesgo Suicida (ARSUIC) cuya principal intervención es una cita prioritaria después de cada intento de suicidio para favorecer la adherencia al seguimiento ambulatorio.
3. La implementación de ARSUIC redujo el tiempo mediano entre alta y primera consulta ambulatoria de 8,5 a 6 días, lo que indica una aceptación sustancial de la intervención en la práctica clínica real.
4. La proporción de pacientes con intento de suicidio que no tuvo una cita ambulatoria en 7 días se redujo del 68% al 50% después de la introducción de ARSUIC. Pese a la aceptación sustancial del programa, la mitad de pacientes no accedieron a la cita prioritaria antes del límite temporal objetivo.
5. Después de instaurar este programa en 2012, tanto la tasa de intento de suicidio por persona-año como la proporción de intentos que correspondían a reintentos se redujeron de manera progresiva en los años posteriores.
6. En comparación con el anterior tratamiento habitual, los individuos que recibieron la intervención ARSUIC tuvieron un 24% menos de riesgo de reintento en un seguimiento de tres años. Estos resultados sugieren que la intervención fue efectiva, reduciendo el riesgo de suicidio tras un intento.
7. En dos áreas sanitarias de la Comunidad de Madrid se implementaron estrategias de intensificación basadas en complementar ARSUIC con contactos adicionales telefónicos y en persona o con psicoterapia.
8. Las intervenciones de intensificación Contacto Aumentado y Psicoterapia conllevaron una reducción adicional del riesgo de suicidio del 40% en un seguimiento de un año. La

diferencia de efectividad entre estas dos estrategias de intensificación resultó prácticamente indetectable.

9. En comparación con ARSUIC, tanto Contacto Aumentado como Psicoterapia incurrieron en costes adicionales que no superan los límites razonables de disposición a pagar por intento de suicidio evitado.
10. Dado que Contacto Aumentado supuso un coste menor y una efectividad similar, minimizó ligeramente los costes en comparación con Psicoterapia.
11. Como aproximación general a una población no seleccionada de personas que han intentado suicidarse, aumentar la tasa de contacto con los profesionales de servicios de salud mental es, probablemente, la estrategia de intensificación más coste-efectiva.
12. Para guiar la decisión de qué intervención es más adecuada para cada paciente, quedan pendientes la identificación de predictores individuales de buena respuesta clínica a cada tratamiento y el estudio del impacto económico del uso de psicoterapia a pacientes seleccionados.

8. Tables and figures

Table 1. Demographic characteristics and distribution of cases of suicide attempt per study year

Year	N	Age in years: P50 (DS)	Male N(%)	Female N(%)
2012	199	42,66 (14,59)	53 (26,6%)	146 (73,4%)
2013	242	42,85 (17,46)	82 (33,9%)	160 (66,1%)
2014	265	39,08 (15,89)	76 (28,7%)	189 (71,3%)
2015	180	39,86 (15,93)	71 (39,4%)	109 (60,6%)
2012-15	886		282 (31,8%)	604 (68,2%)

Table 2. Percentage of suicide attempts with time to first outpatient visit following discharge \leq or $>$ 7 days ($p=0.002$) and percentage of cases with no outpatient follow-up ($p<0.001$).

Year	Total	Follow-up \leq 7 days	Follow-up $>$ 7 days	No follow-up
2012	197	63 (32%)	134 (68%)	1%
2013	231	112 (48,5%)	119 (51,5%)	4,5%
2014	242	110 (45,5%)	132 (54,5%)	8,7%
2015	160	77 (48,1%)	83 (51,9%)	11,1%
2012-15	830	362 (43,6%)	468 (56,4%)	

Table 3. Baseline clinical and sociodemographic covariates of the 2,347 episodes attempted by the 1,775 study subjects, globally and divided by period of treatment. P-values are obtained from Student's T test for the quantitative covariates and Pearson's Chi-square test for the qualitative ones. (ED = Emergency Department, ICD-10 = International Classification of Diseases 10th revision, F10-19= Mental and behavioral disorders due to psychoactive substance use, F20-29 = Schizophrenia, schizotypal and delusional disorders, F30-39 = Mood (affective) disorders, F40-48 = Neurotic, stress-related and somatoform disorders, F50-59 = Behavioral syndromes associated with physiological disturbances and physical factors, F60-69 = Disorders of adult personality and behavior.)

		Total	Control period	Intervention period	P
Total study subjects	N (%)	1,775	875 (49.3)	900 (50.7)	
Total suicide attempts	N (%)	2,347	1,176 (50.1)	1,171 (49.9)	
Age in years	Mean (SD)	40.5 (16.7)	40.2 (16.3)	40.8 (17.0)	0.36
Female	N (%)	1602 (68.3)	814 (69.2)	788 (67.3)	0.32
Personal history of a psychiatric disorder	N (%)	1735 (73.9)	883 (75.1)	852 (72.7)	0.00
ICD-10 F10-19	N (%)	880 (37.5)	412 (35.5)	468 (40.0)	
ICD-10 F20-29	N (%)	162 (6.9)	98 (8.3)	64 (5.4)	
ICD-10 F30-39	N (%)	925 (39.4)	441 (37.5)	484 (41.0)	
ICD-10 F40-49	N (%)	880 (37.5)	416 (35.4)	464 (39.6)	
ICD-10 F50-59	N (%)	145 (6.2)	65 (5.5)	80 (6.8)	
ICD-10 F60-69	N (%)	401 (17.1)	194 (16.5)	207 (17.7)	
Personal history of suicide attempts	N (%)	1137 (48.4)	571 (48.6)	566 (48.3)	0.07
Concurrent alcohol/ drug abuse	N (%)	945 (40.3)	460 (39.1)	485 (41.4)	0.00
Family support	N (%)	1604 (68.3)	732 (62.3)	872 (74.5)	0.00
Admitted after ED discharge	N (%)	528 (22.5)	288 (24.5)	240 (20.5)	0.00

Table 4. Risk of relapse during the follow-up, derived from a Cox proportional hazard model including time to relapse as the outcome and the clinical and sociodemographic covariates as predictors. Control period is the reference. Multivariate model A retained those covariates associated to the $p \leq 0.05$ significant level. Model B included additional covariates, relevant according to the proposed causal frame.

	Relapsed during follow-up N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	
			Model A	Model B
Control period (REF)	283 (24.1)	1	1	1
Intervention period	214 (18.3)	0.72 (0.60-0.82)	0.76 (0.62-0.93)	0.69 (0.54-0.87)
Female	609 (38.0)	1.17 (0.96-1.42)	1.30 (1.03-1.68)	1.30 (1.02-1.65)
Personal history of psychiatric disorder	757 (43.6)	3.21 (2.30-4.47)	1.99 (1.33-2.99)	2.03 (1.30-3.18)
Personal history of suicide attempts	627 (55.2)	2.71 (2.20-3.34)	2.29 (1.77-2.96)	2.32 (1.75-3.06)
Concurrent alcohol/ drug abuse	468 (49.5)	1.77 (1.46-2.15)	1.55 (1.25-1.90)	1.58 (1.26-1.98)
Family support	640 (39.9)	0.64 (0.49-0.83)	0.74 (0.56-0.99)	0.66 (0.49-0.89)
Number of relapses	-	1.39 (1.36-1.42)	1.35 (1.31-1.39)	1.33 (1.29-1.37)
Admitted after ED discharge	248 (47.0)	1.14 (0.93-1.40)	-	1.20 (0.94-1.53)
Age in years	-	1.00 (0.99-1.00)	-	0.99 (0.99-1.00)

Table 5. Baseline clinical and sociodemographic covariates of the 1,492 study subjects, globally and divided by interventions. P-values are obtained from Pearson's Chi-square test or Fisher's exact test for qualitative covariates and Wilcoxon's sign test for quantitative ones. (ICD-10 = International Classification of Diseases 10th revision, F00-F09 = Organic, including symptomatic, mental disorders, F10-19 = Mental and behavioral disorders due to psychoactive substance use, F20-29 = Schizophrenia, schizotypal and delusional disorders, F30-39 = Mood (affective) disorders, F40-48 = Neurotic, stress-related and somatoform disorders, F50-59 = Behavioral syndromes associated with physiological disturbances and physical factors, F60-69 = Disorders of adult personality and behavior.)

	Total N (%)	TAU	Psychotherapy	Enhanced Contact	X2/F	P
Total suicide attempters	1,492	788 (52.8)	523 (35.1)	181 (12.1)		
Age in years (Mean±SD)	40.9 (17.1)	41.0 (18.0)	40.3 (16.6)	42.6 (14.5)	1.25	0.29
Female	1,040 (69.7)	540 (68.5)	360 (68.8)	140 (77.4)	5.77	0.06
Personal history of a psychiatric disorder	976 (65.4)	554 (70.3)	255 (48.8)	166 (91.7)	0.00	0.000
Main diagnosis at discharge						
No diagnosis	190 (12.7)	110 (13.9)	74 (14.15)	6 (3.3)	404.41	0.000
Organic, including symptomatic, mental disorders	11 (0.8)	6 (0.9)	5 (0.9)	0 (0.0)		
Mental and behavioral disorders due to psychoactive substance use	172 (12.5)	94 (13.8)	68 (13.0)	10 (5.7)		
Schizophrenia, schizotypal and delusional disorders	28 (2.0)	15 (2.2)	12 (2.3)	1 (0.6)		
Mood (affective) disorders	406 (29.4)	304 (44.7)	66 (12.6)	36 (20.3)		
Neurotic, stress-related and somatoform disorders	429 (31.1)	150 (22.1)	208 (39.8)	71 (40.1)		
Behavioral syndromes associated with physiological disturbances and physical factors	37 (2.7)	14 (2.1)	22 (4.2)	1 (0.6)		
Disorders of adult personality and behavior	219 (15.9)	95 (14.0)	68 (13.00)	56 (31.6)		
Personal history of suicide attempts	583 (39.1)	272 (34.5)	145 (27.7)	85 (47.0)	246.21	0.00
Concurrent alcohol/ drug abuse	446 (29.9)	281 (35.7)	80 (15.3)	85 (47.0)	91.19	0.00
Cohabitation	1,250 (83.7)	639 (81.1)	458 (87.4)	153 (84.5)	9.30	0.01
Immigrant	483 (32.4)	132 (16.8)	200 (38.2)	151 (83.4)	322.47	0.00
Comorbid medical conditions	551 (36.9)	481 (61.0)	39 (7.4)	31 (17.1)	422.87	0.00

Table 6. Risk of relapse during the follow-up, derived from a Cox proportional hazard model including time to relapse as the outcome and the clinical and sociodemographic covariates as predictors. Treatment as usual (TAU) is the reference. The multivariate model is age and gender-adjusted and includes variables significant to the $p \leq 0.05$ level following a non-automatic adjustment method. (ICD-10 = International Classification of Diseases 10th revision, F10-19= Mental and behavioral disorders due to psychoactive substance use, F20-29 = Schizophrenia, schizotypal and delusional disorders, F30-39 = Mood (affective) disorders, F40-48 = Neurotic, stress-related and somatoform disorders, F50-59 = Behavioral syndromes associated with physiological disturbances and physical factors, F60-69 = Disorders of adult personality and behavior.) (* $p \leq 0.05$; ** $p \leq 0.01$)

	Relapsed during follow-up N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
TAU	90 (11.4)	1	1
Psychotherapy	29 (5.5)	0.47 (0.31-0.72) **	0.62 (0.40-0.97) *
Enhanced Contact	14 (7.7)	0.66 (0.38-1.16)	0.56 (0.32-1.00) *
Age in years		0.99 (0.98-1.00)	0.99 (0.98-1.00)
Female gender		1.27 (0.86-1.87)	1.32 (0.88-1.98)
Immigrant		0.68 (0.46-1.00) *	-
Cohabitation		1.10 (0.68-1.77)	-
Personal history of a psychiatric disorder		1.86 (1.24-2.80) **	-
Diagnosis at discharge			
No diagnosis		0.67 (0.37-1.21)	-
Mental and behavioral disorders due to psychoactive substance use		1.38 (0.86-2.22)	-
Mood (affective) disorders		1.70 (1.20-2.42) **	1.60 (1.10-2.32) **
Neurotic, stress-related and somatoform disorders		0.35 (0.21-0.58) **	-
Disorders of adult personality and behavior		1.52 (1.00-2.32) *	1.82 (1.14-2.91)**
Personal history of suicide attempts		1.89 (1.34-2.65) **	1.63 (1.15-2.31) **
Concurrent alcohol/ drug abuse		1.77 (1.35-2.67) **	1.64 (1.13-2.38) **
Comorbid medical condition		1.73 (1.23-2.43) **	-

Table 7: Risk of relapse during the follow-up, derived from a Cox proportional hazard model including time to relapse as the outcome and the clinical and sociodemographic covariates as predictors. Treatment as usual (TAU) is the reference. This alternative multivariate model is age and gender-adjusted and includes personal history of a psychiatric disorder, instead of specific diagnostic groups. (* $p \leq 0.05$; ** $p \leq 0.01$)

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
TAU	1	1
Psychotherapy	0.47 (0.31-0.72) **	0.56 (0.37-0.87)**
Enhanced Contact	0.66 (0.38-1.16)	0.56 (0.31-0.98)*
Age in years	0.99 (0.98-1.00)	0.99 (0.98-1.00)
Female gender	1.27 (0.86-1.87)	1.35 (0.90-2.01)
Immigrant	0.68 (0.46-1.00) *	-
Cohabitation	1.10 (0.68-1.77)	-
Personal history of a psychiatric disorder	1.86 (1.24-2.80) **	1.42 (0.92-2.19)
Personal history of suicide attempts	1.89 (1.34-2.65) **	1.56 (1.09-2.23)**
Concurrent alcohol/ drug abuse	1.77 (1.35-2.67) **	1.54 (1.06-2.22)*
Comorbid medical condition	1.73 (1.23-2.43) **	-

Table 8. Risk of relapse during the follow-up, stratified into 3 patient groups: male, female ≤ 35 years of age and female > 35 years of age. The multivariate model is derived from an age and gender-adjusted Cox proportional hazard multivariate model, with time to relapse as the outcome and treatment as usual (TAU) as the reference and includes the same covariates as the multivariate model in table 2. (ICD-10 = International Classification of Diseases 10th revision, F30-39 = Mood (affective) disorders, F50-59 = Behavioral syndromes associated with physiological disturbances and physical factors, F60-69 = Disorders of adult personality and behavior.) (* $p \leq 0.05$; ** $p \leq 0.01$)

	Male	Female ≤ 35 y	Female > 35 y
TAU	1	1	1
Psychotherapy	0.62 (0.37-1.04)	0.57 (0.27-1.20)	0.65 (0.32-1.34)
Enhanced Contact	0.57 (0.31-1.08)	0.66 (0.22-1.96)	0.54 (0.25-1.19)
ICD-10 F30-39	1.54 (0.96-2.32)	1.61 (0.75-3.43)	1.54 (0.83-2.85)
ICD-10 F60-69	2.09 (1.25-3.51)	1.91 (0.75-3.43)	2.29 (1.11-4.70)*
Personal history of suicide attempts	1.73 (1.16-2.59)**	1.48 (0.79-2.77)	1.93 (1.13-3.29) *
Concurrent alcohol/ drug abuse	1.73 (0.98-2.32)	1.96 (0.45-2.02)	1.64 (1.14-3.35) *
N (%)	452 (30.3%)	452 (30.3%)	588 (39.4%)

Table 9. Comparative effectiveness estimates

	Relapsed during follow-up N (%)	Adjusted HR (95% CI)	Adjusted relapse rate	Inferior limit of the 95% CI	Superior limit of the 95% CI
TAU	90 (11.4)	1 (Ref.)	11.4	10.2	12.6
Enhanced Contact	29 (5.5)	0.56 (0.31-0.98)	6.4	3.5	11.2
Psychotherapy	14 (7.7)	0.56 (0.37-0.87)	6.4	4.2	9.9

TAU = Treatment as Usual.

Adjusted Hazard Ratio (HR) values were derived from a multivariable Cox proportional hazards model where time to relapse was the outcome, intervention group was the independent variable and age, sex, history of a psychiatric disorder, history of suicide attempts and concurrent alcohol or drug abuse were covariates.

Table 10. Cost-effectiveness model input data

Parameter	Base case	Sensitivity analyses value distribution			Source	
		Deterministic Sensitivity Analysis		Probabilistic sensitivity analysis value or distribution		
		Most favorable scenario	Least favorable scenario			
Suicide attempt probability						
TAU	0.114	0.102	0.126	β ($\alpha = 0.28, \beta = 2.14$)	Martínez-Alés et al., 2019	
Enhanced Contact	0.064	0.035	0.112	β ($\alpha = 0.28, \beta = 2.14$) * 0.56		
Psychotherapy	0.064	0.042	0.099	β ($\alpha = 0.28, \beta = 2.14$) * 0.56		
Intervention costs						
TAU ^a	€ 311	€ 264	€ 358	€ 311	EHR	
Enhanced Contact ^b	€ 779	€ 662	€ 896	€ 779	Protocol	
Psychotherapy ^c	€ 975	€ 829	€ 1121	€ 975		
Relapse costs						
ED visit	€ 190	€ 162	€ 219	All prorated direct costs: Normal, mean (SD): € 1106 (369) * 0.994	EHR and official sources	
Ambulance	€ 452	€ 384	€ 520			
In-patient hospitalization ^d	€ 3973	€ 3377	€ 4569			
Death ^e	€ 631680	€ 536928	€ 726432			€ 631680 * 0.006
Sick leave ^f	€ 9363	€ 7956	€ 10767			Normal, mean (SD): € 9363 (3122) * 0.23 * 0.994

All economic amounts come from official costs of the Community of Madrid (BOCM) except for average wages, retrieved from the National Institute of Statistics (INE).

^a 1st outpatient visit (€ 91) + 4 follow-ups (€ 220)

^b TAU + 3 specialized visits (€ 438) + 3 telephone calls (€ 30)

^c TAU + 8 psychotherapy sessions (€ 664)

^d The proportion of admissions was: 73% psychiatric ward, 20% medical ward, 7% intensive care unit

^e For deceased participants, average years of life lost (65-37) * Average annual wage (€ 22,560)

^f For participants undergoing sick leave, average duration in days (155.6) * Average daily wage (€ 60.2)

Table 11. Incremental Cost-effectiveness Ratios (ICERs) estimates per re-attempt avoided, calculated from a societal perspective

ICER	Base case scenario	Most favorable scenario	Least favorable scenario
Enhanced Contact vs. TAU	€ 2340	€ -27	€ 30356
Psychotherapy vs. TAU	€ 6260	€ 3450	€ 20186

Figure 1: Directed Acyclic Graph representing the causal framework under which models were conducted.

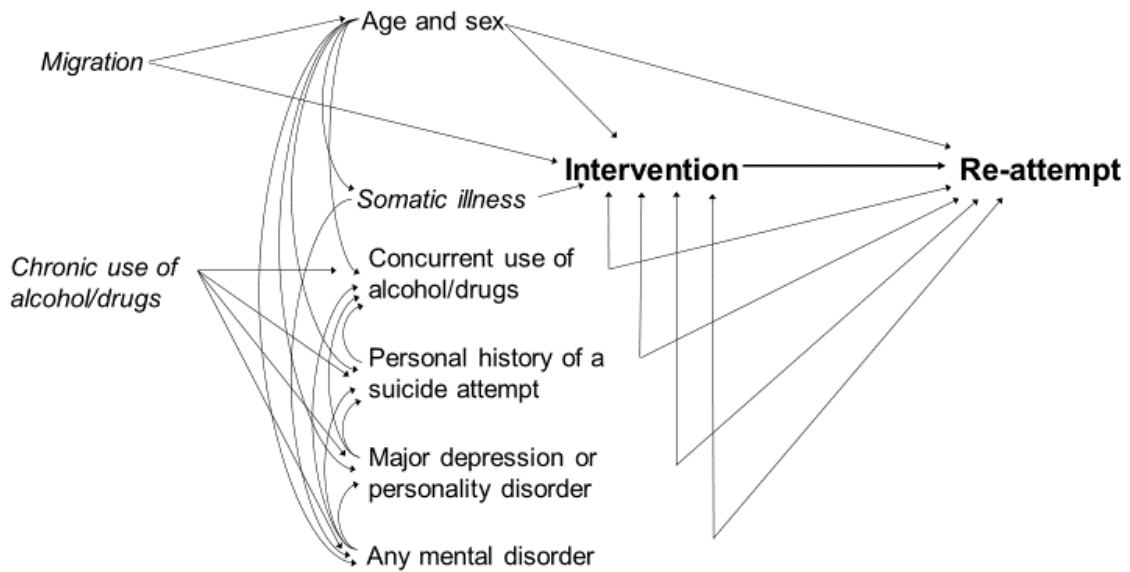


Figure 2: Time between discharge and first outpatient visit, within a maximum 1-month follow-up, per study year. Results in median±standard deviation are P50±SD 2012: 8,5±7,57; 2013: 6±7,31; 2014: 7±6,91; 2015: 7±6,54; $p=0,03$.

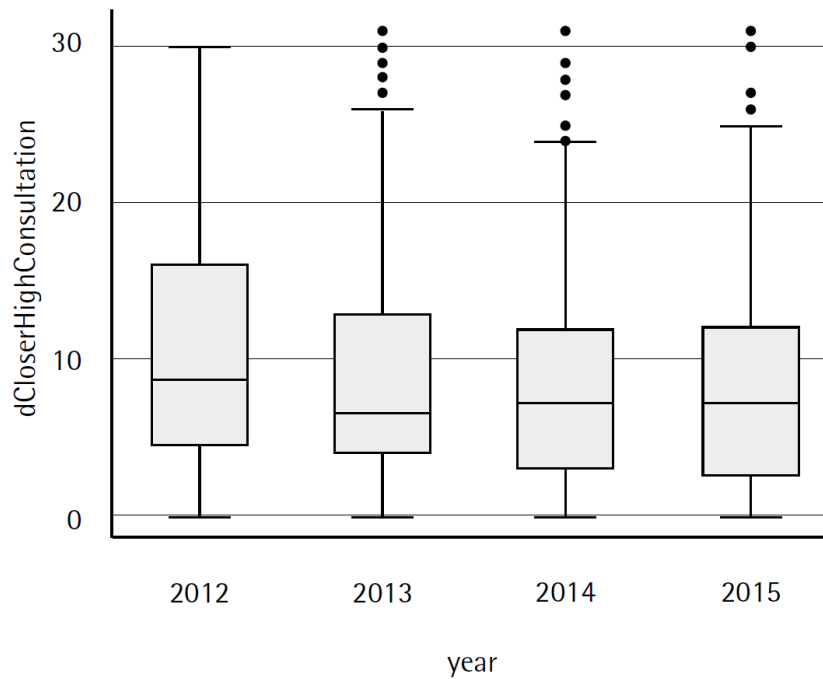


Figure 3: Percentage of suicide attempts that correspond to a reattempt per study year. $P=0.002$

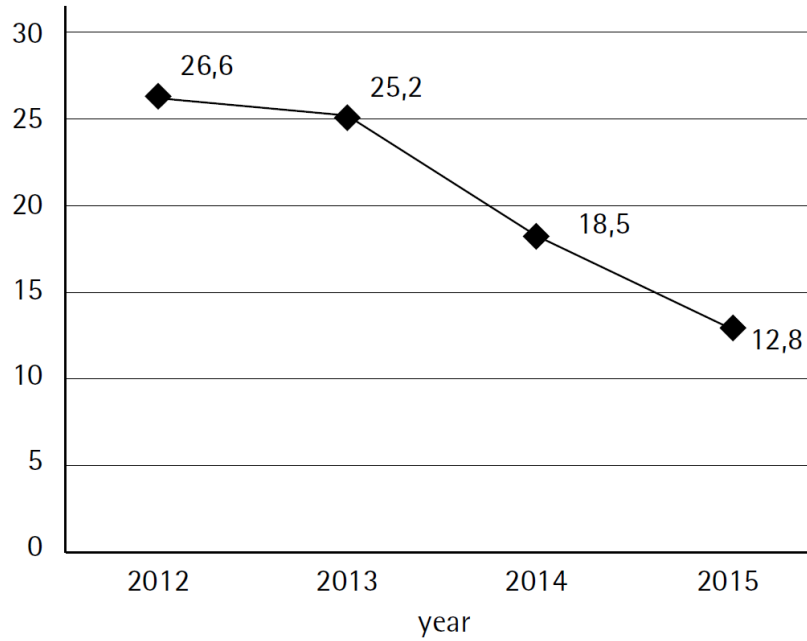


Figure 4: Suicide attempt rate per person-year. The difference between the logarithms of the rates 2012-2015 is statistically significant at an adjusted p-value level = 0.017

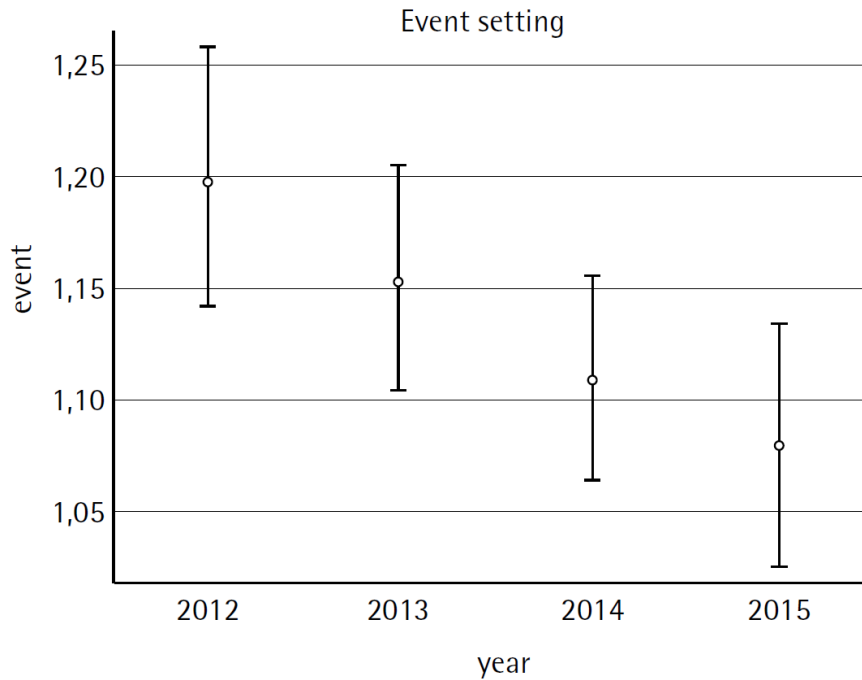


Figure 5: Time between hospital discharge following a suicide attempt and a subsequent suicide attempt, within a maximum 1-year follow-up, per study year. P=0.01

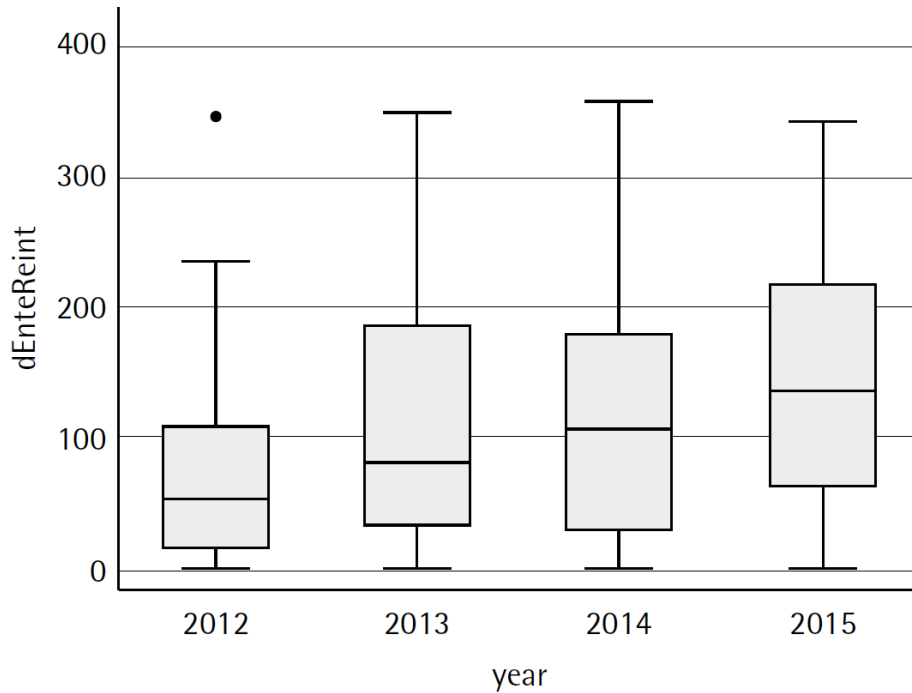


Figure 6. Distribution of repeated suicide attempts among subjects across study periods.

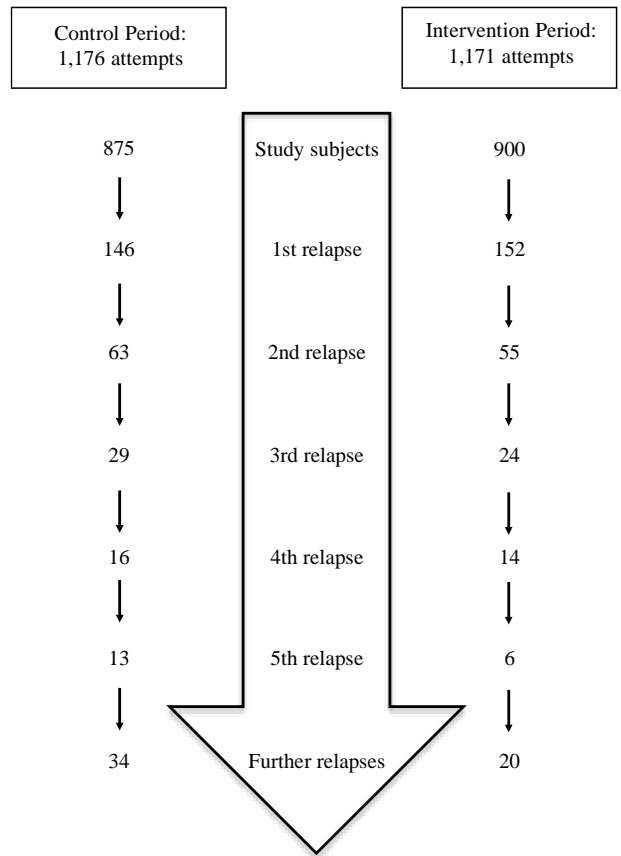
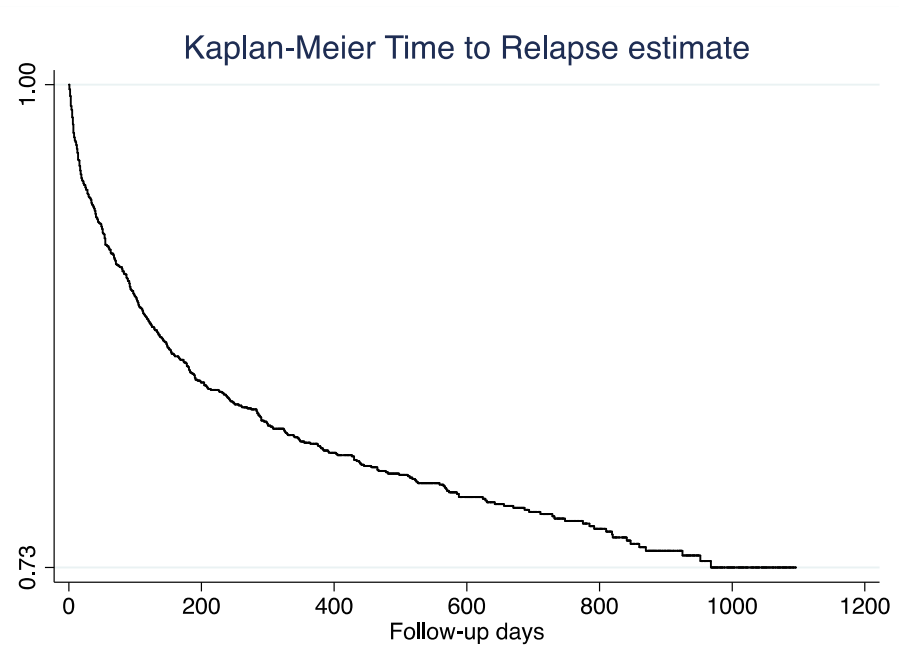


Figure 7. Kaplan-Meier survival function estimates. (A) Shows the graphic representation of time to relapse estimate including every suicide attempt recorded between 2010 and 2015. (B) Shows the graphic representation of time to relapse estimates divided by treatment period. Differences are significant with a log-rank test's $P < 0.001$.

A.



B.

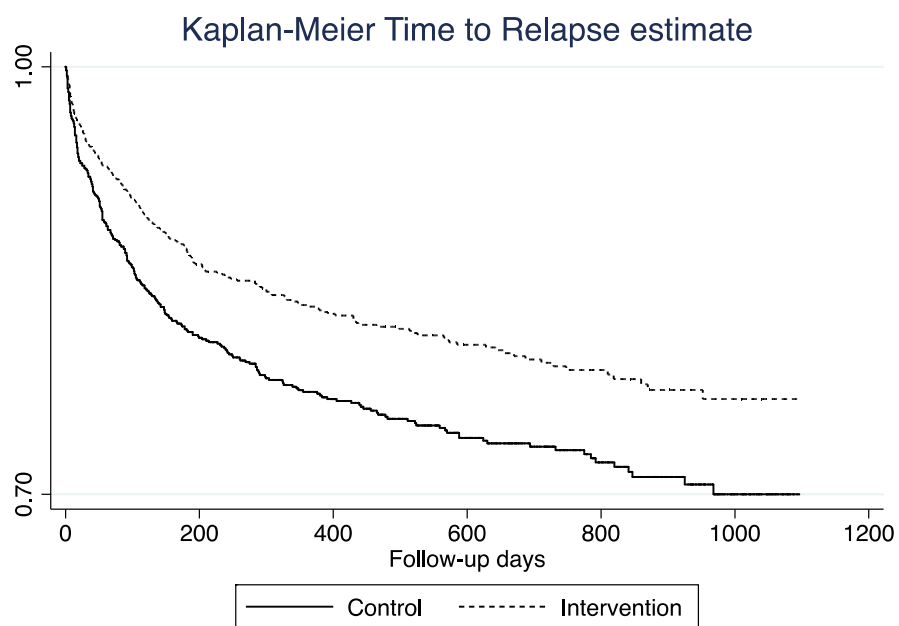


Figure 8. Graphically represents Kaplan-Meier survival function estimates by intervention. (A) Differences between Treatment as Usual (TAU) and Psychotherapy are significant with a log-rank test's $P < 0.01$. (B) After adjustment by sex, gender, concurrent alcohol or drug abuse, personal history of suicide attempts, presence of a mood disorder diagnosis and presence of a personality disorder diagnosis, differences between Treatment as Usual (TAU) and both Enhanced Contact and Psychotherapy are significant with a log-rank test's $P < 0.05$.

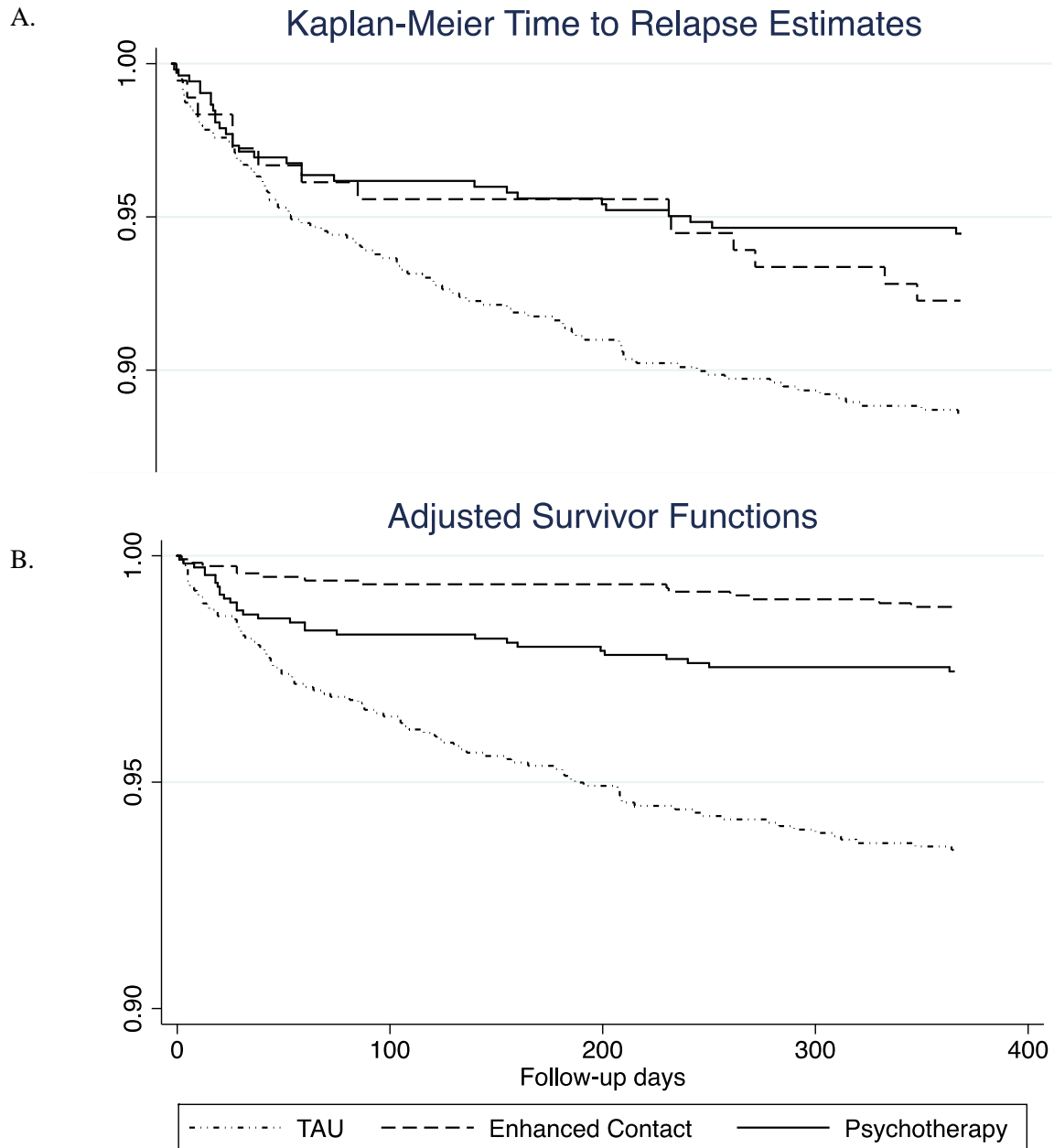


Figure 9. Decision tree structure for each strategy. Intermediate nodes include the probability of each potential outcome. Final nodes include the cost incurred from a societal perspective.

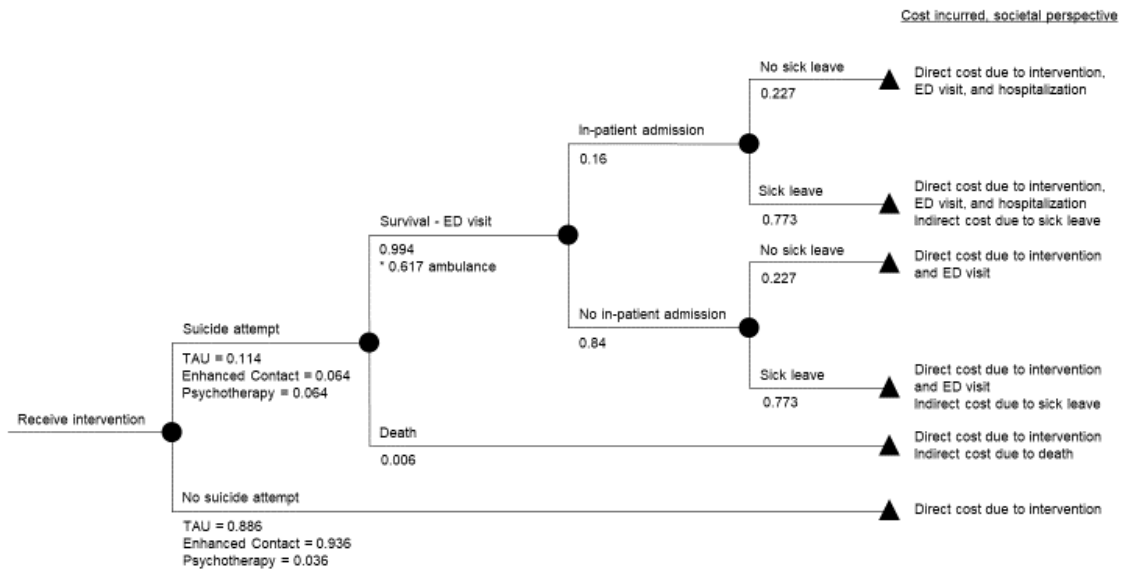
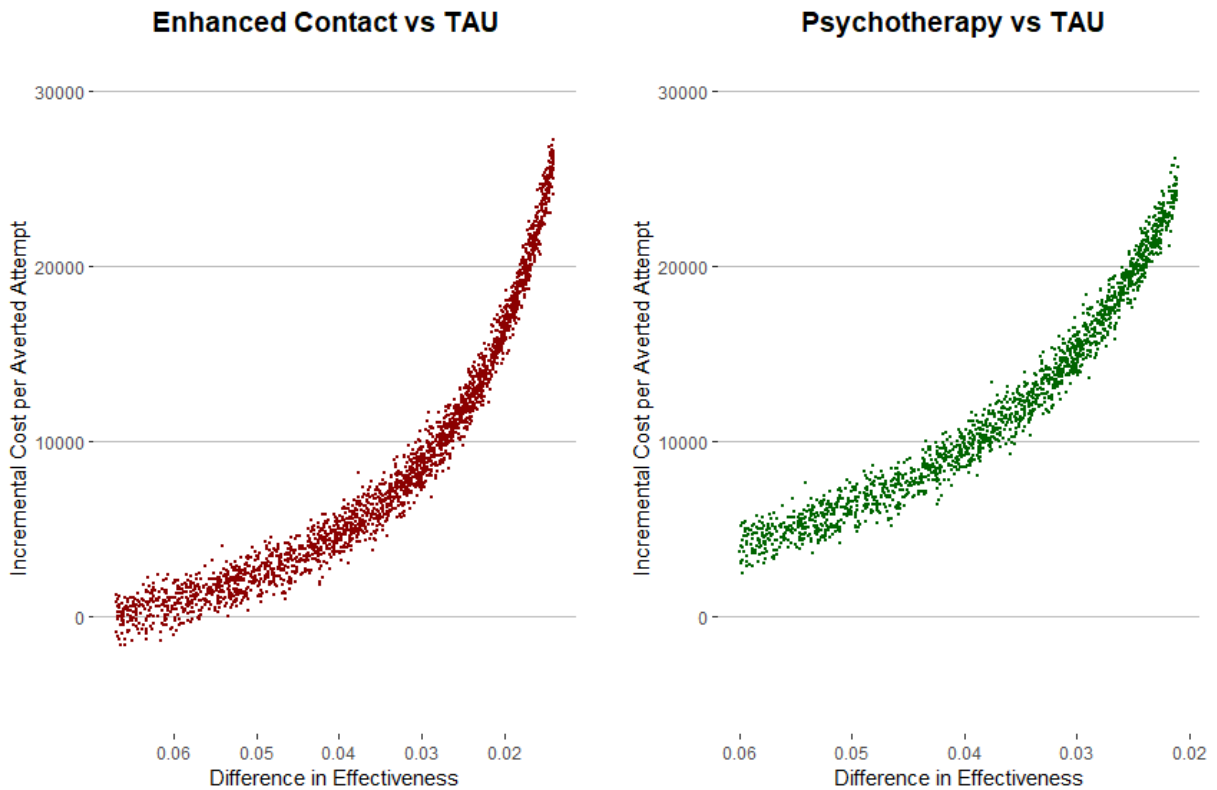


Figure 10. Results from the probabilistic sensitivity analysis, indicating the results of 10,000 simulations based on the parameters indicated on table 10.



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10. Attached materials

10.1 International mention

10.2 Institutional Review Board approval

10.3 Published articles

10.3.1 Original research articles that form the dissertation (* denotes co-first authorship)

Citation	2018 Impact factor (quartile)
E Jimenez-Sola*, <u>G Martínez-Alés*</u> , E Román, MP Sánchez, B Rodríguez, C de Dios, MF Bravo. Implementation of a suicide prevention program in Madrid, Spain: the ARSUIC experience [Implementación de un programa de prevención de suicidio en Madrid, España: la experiencia ARSUIC]. Act Esp Psiq 2019;47(6):229-35.	1.5 (Q3)
<u>G Martínez-Alés</u> , E Román, E Jiménez, MP Sánchez, B Rodríguez, C de Dios, MF Bravo. An emergency-department initiated intervention to lower relapse risk after suicide attempts. Suicide Life Threat Behav 2019, 9(6):1587-1599 doi: 10.1111/sltb.12542	3.0 (Q1)
<u>G Martínez-Alés</u> , R Angora, M Barrigón, et al. A real-world effectiveness study comparing a priority appointment, an enhanced contact intervention and a psychotherapeutic program following attempted suicide. J Clin Psychiat 2019; 80(2). doi 10.4088/JCP.18m12416	4.3 (Q1)
<u>G Martínez-Alés</u> , B Cruz-Rodríguez, P Lázaro, A Domingo-Relloso, M Barrigón, L Villoria, R Angora, R Rosenheck, B Stanley, M Navío, E Baca-García, MF Bravo-Ortiz. Real-world cost-effectiveness of a priority appointment, a brief contact intervention and a psychotherapeutic program for secondary prevention following attempted suicide.	<i>Under review</i>

10.3.2 Articles elaborated within the doctoral program that directly inform the introduction and methods sections of the dissertation

Citation	2018 Impact factor (quartile)
E Susser, <u>G Martínez-Alés</u> . Putting psychoses into sociocultural context: a study in 17 locations. <i>JAMA Psychiat</i> 2018; 75(1): 9-10 doi: 10.1001/jamapsychiatry.2017.3541	15.9 (Q1, D1)
<u>G Martínez-Alés</u> , F Mascayano, MF Bravo. Suicide: contexts and persons [Suicidio: contextos y personas]. <i>Rev Psiquiatr Salud Men</i> 2018;12(4):253-254. doi: 10.1016/j.rpsm.2018.05.001	2.9 (Q2)
<u>G Martínez-Alés</u> , E Baca-García, MF Bravo. Suicidal individuals and suicidal populations? [¿Individuos suicidas y poblaciones suicidas?] <i>Rev Esp Med Prev</i> 2018; 2(23): 44-6	NA
T López-Cuadrado, <u>G Martínez-Alés</u> , C Bouza. The effect of dementia on risk of acute organ dysfunction, mortality and healthcare resources in hospitalized elderly patients with sepsis in Spain: an observational population-based study. <i>PloS One</i> 2019; 14(2):e0212196 doi: 10.1371/journal.pone.0212196	2.8 (Q1)
<u>G Martínez-Alés</u> , KM Keyes, E Baca-García. Beyond statistical significance: An underrated suicide prevention intervention. <i>J Clin Psychiat</i> 2019; 80(4) doi: 10.4088/JCP.19lr12814	4.3 (Q1)
<u>G Martínez-Alés</u> , KM Keyes. Fatal and non-fatal self-injury in the United States: current trends and innovations in prevention. <i>Current Psych Rep</i> 2019 2019; 21(10):104 doi: 10.1007/s11920-019-1080-6	3.8 (Q1)
<u>G Martínez-Alés</u> C Bouzá, M Olfson, T López-Cuadrado. Invasive Mechanical Ventilation for People with Severe Mental Disorders: Recent Trends in Incidence and In-Hospital Mortality. <i>Intensive Care Medicine</i> 2019 [<i>in press</i>] doi 10.1007/s00134-019-05850-4	18.9 (Q1, D1)
<u>G Martínez-Alés</u> , D Hernández-Calle, N Khauli, KM Keyes. Why are suicide rates increasing in the United States? Towards a multi-level reimagination of suicide prevention. <i>Current Topics in Behavioral Neurosciences</i> 2019 [<i>accepted</i>].	20.3 (Q1, D1)
C Bouzá, <u>G Martínez-Alés</u> , T López-Cuadrado. Effect of dementia on the incidence, short-term outcomes and resource utilization of invasive Mechanical Ventilation in the elderly: a nationwide population-based study (2000-2013). <i>Critical Care</i> 2019; 23(1):291 doi: 10.1186/s13054-019-2580-9	6.9 (Q1, D1)
D Hernández-Calle, <u>G Martínez-Alés</u> , E Román-Mazuecos, B Rodríguez-Vega, MF Bravo-Ortiz. Prevention over prediction: the psychiatrist's challenge when assessing suicide risk in the emergency department [Prevención sobre predicción: el reto del psiquiatra en la valoración de riesgo autolítico en urgencias]. <i>Rev Psiquiatr Salud Men</i> 2020 [<i>accepted</i>]	2.9 (Q2)

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Implementation of a suicide risk prevention program in the Autonomous Community of Madrid. The ARSUIC experience

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Introduction. This study evaluates the degree of compliance and effectiveness of the ARSUIC Suicide Risk Care Program. ARSUIC seeks to reduce the relapse risk that follows a suicide attempt by scheduling a high priority outpatient visit following hospital discharge.

Method. Hospital-based retrospective study conducted between years 2012 and 2015. We included every suicide attempt treated at the La Paz University Hospital's mental healthcare resources network. We estimated the time between hospital discharge and the first outpatient visit; the proportion of visits that fulfill the program's objective – a follow-up within a maximum of 7 days; the suicide attempt rate; and the percentage of attempts corresponding to relapses, by study year.

Results. After program deployment, median time between discharge and the first visit decreased from 8.5 to 6 days, and the percentage of visits that fulfill the program's objective increased from 32 to 48.5%. Between years 2012 and 2015, the suicide attempt rate per person and year decreased from 1.20 to 1.08 and the proportion of attempts corresponding to relapses from 26.6% to 12.8%.

Conclusion. Implementing the ARSUIC Program lowered the time between discharge and the first outpatient visit following a suicide attempt. The proportion of suicide attempts due to relapses and the suicide attempt rate per person decreased progressively. The program fulfillment proportion was under 50%, suggesting between-user differences regarding their effective access to the program.

Key words: Suicide, Mental health, Program evaluation, Implementation
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Implementación de un programa de prevención del riesgo de suicidio en la Comunidad Autónoma de Madrid. La experiencia ARSUIC

Introducción. Este estudio evalúa el grado de cumplimiento y efectividad del programa ARSUIC de Atención al Riesgo Suicida, cuyo objetivo es reducir el riesgo posterior al intento de suicidio facilitando una cita ambulatoria de alta prioridad después del alta hospitalaria.

Metodología. Estudio retrospectivo de base hospitalaria conducido, entre 2012 y 2015, en todos los casos de intento de suicidio atendidos en la red de recursos de psiquiatría del Hospital Universitario La Paz. Se obtienen estimadores del tiempo hasta la primera consulta después del alta, de la proporción de citas que cumple el objetivo del programa de ser atendidos en un máximo de 7 días, de la tasa de intento de suicidio y del porcentaje de intentos que corresponde con un reintento, en cada year de estudio.

Resultados. Después de la implementación del programa, la mediana de tiempo entre el alta y la primera consulta baja de 8,5 a 6 días y el porcentaje de citas que cumplen el objetivo aumenta de 32 a 48,5%. Entre 2012 y 2015, la tasa de intentos de suicidio por paciente y year se reduce de 1,20 a 1,08, y el porcentaje de intentos que corresponde con reintentos de 26,6 a 12,8%.

Conclusión. La implementación del Programa ARSUIC ha reducido el tiempo entre el alta después de un intento de suicidio y la primera cita ambulatoria. Han disminuido los intentos de suicidio debidos a reintentos y la tasa de intentos por paciente y year. El porcentaje de cumplimiento menor al 50% sugiere diferencias interindividuales en el acceso efectivo al programa.

Palabras clave: Suicidio, Salud mental, Evaluación de programas, Implementación

INTRODUCTION

Almost 1 million people die by suicide every year¹, and it is the second most frequent cause of death among youth². In Spain, suicide is the most frequent external cause of death, with an annual incidence rate ranging between 11.88 per 100,000 men and 4.05 per 100,000 women³. Suicide risk factors interact in complex hierarchical networks^{4,5}. Among them, a personal history of suicide attempting stands out as the main clinical predictor of subsequent reattempt and death by suicide⁶. It is estimated that having attempted suicide increases lifetime risk of death by suicide by 30 times, and antecedes 1 in 2 deaths by suicide⁷⁻⁹. In addition, suicide attempt, an entity up to 30 times more frequent than death by suicide¹⁰, constitutes itself an identifiably clinical challenge, with remarkable direct and indirect costs and an increasing incidence across the globe^{11,12}.

Suicide prevention can be exercised at different intervention levels¹³. At the population-level, several measures have proved protective: in general terms, these strategies seek to limit the access to potentially lethal methods. Examples include limiting the content in the packaging of drugs commonly used in overdose, such as acetaminophen or benzodiazepines¹⁴, or limiting the access to suicide by jumping hotspots¹⁵. Individual-level prevention is exercised through clinical interventions directed towards individuals at high risk of suicide. The healthcare setting is considered adequate for risk detection, since up to 45% who die by suicide have been seen by a physician during the previous month¹⁶. Among high-risk patients, those with a prior suicide attempt stand out¹⁷, in particular immediately after hospital discharge, a period that entails an extraordinary reattempt risk¹¹. Best available evidence corresponds to contact maintenance with high-risk individuals, usually using "gatekeepers" – people who can be accessed during suicidal crises¹⁸. A recent meta-analysis of randomized controlled trials found that WHO-BIC (Brief Intervention and Contact), a program aimed at enhancing contacts between practitioners and suicidal clients, is effective at lowering suicide reattempts and death by suicide¹⁹. The same meta-analysis found psychotherapeutic interventions not effective. The ED-SAFE randomized trial, conducted in the United States, concluded that an Emergency Department-initiated intervention that clarified potential resources for suicidal crises effectively reduced new attempts and deaths²⁰.

In the Autonomous Community of Madrid, the 2010-2014 Strategic Mental Health Plan highlighted suicide as a fundamental line of work, and selected the following related objectives: establishing an epidemiologic surveillance system of suicide, developing a clinical gold-standard for people at high risk, and enhancing research on suicidal behaviors²¹. The Suicide Risk Care Program (ARSUIIC for its Spanish acronym) was specifically deployed to prioritize the care of

suicidal attempters, in order to reduce their reattempt risk. Although the ARSUIIC program is active in all hospitals in the Autonomous Community of Madrid, results have not been reported yet. The objective of this study is to evaluate the program by estimating the degree of implementation, fulfillment and effectiveness.

METHODS

Study design, context and subjects

Observational, retrospective, hospital-based study. La Paz University Hospital serves a catchment area of 525,501 people in the North of Madrid. The mental healthcare system includes a variety of outpatient and inpatient resources, such as the Emergency Department (ED), the psychiatric inpatient unit, and several Community Mental Healthcare Centers (CMHC). Between Jan 1st 2012 and Dec 31st 2015, 1,633 patients received medical and mental healthcare at the ED due to a suicidal attempt. Patients admitted to the ED following a suicide attempt can be either discharged from the ED or admitted to the hospital. If the attempt leads to relevant medical damage, the patient will require admission to a medical ward, where an interconsultation-liaison psychiatrist will provide psychiatric care after somatic stabilization. If suicide risk remains substantially high after ED/medical ward discharge, the patient can be admitted to the psychiatric inpatient unit. This study featured all suicide attempters discharged from the ED, a medical ward or the psychiatric inpatient unit. In the context of psychiatric emergency care, any self-harm with at least some intention to die as a result is considered a suicide attempt. Hence, we excluded all patients with suicidal ideation who had not committed self-harm. Also, and given the study aim of evaluating the degree of program fulfillment within a specific catchment area, we excluded all subjects seen in our ED who pertained to different areas – these patients are usually referred to their correspondent ED for clinical management before discharge or admission to an inpatient ward. In addition, we excluded patients who officially pertained to the studied area but received treatment at external mental healthcare resources, such as those admitted to a different psychiatric inpatient unit due to a shortage of beds in the studied area's unit or to their personal preference. The study complied with the Declaration of Helsinki and was authorized by La Paz University Hospital's Clinical Research Ethical Committee.

The ARSUIIC Suicide Risk Attention Program

ARSUIIC ensures priority specialized mental healthcare for subjects who have suffered a suicide attempt, by en-

hancing contact with mental healthcare providers during the days following the attempt. The program was implemented during the last trimester of year 2012, when priority specialized medical appointments took a mean 19 days in the Autonomous Community of Madrid²². ARSUIIC's main measure consists on scheduling all suicide attempters to see an outpatient psychiatrist, who does not have specific suicide prevention training, within a maximum of 7 days following discharge. After the appointment, patients go on to their usual periodic appointments. Hence, ARSUIIC does not feature further additional follow-ups, or specific psychotherapeutic/pharmacologic treatments. The key outpatient visit is scheduled before hospital discharge, and the attending physician details the location and date of the visit in the discharge report.

Study variables

Information regarding dates of admission and discharge was obtained from the hospital's electronic healthcare records (EHR). These records are filed as a requirement before any discharge, and they also include sociodemographic variables: (gender, age), and whether the suicide attempt was an index attempt or a reattempt. Information regarding the first outpatient visit following discharge, and whether the patient complied with it, was retrieved from each CMHC's EHR. To evaluate the degree of implementation, we computed the time between hospital discharge and the first CMHC outpatient visit within the first 30 days. By doing so, we prevented other visits, most likely unrelated to the suicide attempt, from biasing our estimates. This bias would have favored most recently registered cases, because their follow-up periods encompass shorter time windows. We studied time-to-first outpatient visit as a continuous variable, as well as an implementation dichotomous variable (proportion of patients actually seen within a maximum 7 days). In addition, we computed the proportion of subjects who did not had an outpatient visit after the attempt. Using the dates of hospital admission and discharge, we were able to calculate the interval of time between attempts in those patients who had more than a suicide attempt during the study period. Then, to estimate the effectiveness of the program, we obtained the time between attempts within the first follow-up year after each attempt, and the suicide attempt rate per person-year in each of the study years.

Statistical analyses

We obtained descriptive statistics of the study population's sociodemographic variables. They were summarized as percentages in categorical variables, and as the median±standard deviation in continuous ones. Then, we calculated:

time between discharge and the first outpatient visit; time between different attempts; and suicide attempt rate per person-year. We tested that continuous variables were followed a parametric distribution using Kolmogorov-Smirnov's test, we studied temporal trends using Pearson's R coefficients, and we tested before-after implementation differences using Student's t-test for repeated measures. Last, we studied time trends in suicide attempt rates per person-year by fitting a generalized linear model (GLM). Inter-annual rate logarithm comparisons were adjusted for multiple comparisons using Bonferroni's method. We conducted all analyses using SPSS v.22 for Windows²³, with the collaboration of La Paz University Hospital's Biostatistical consultants. Graphics were programmed using Stata v. 13 for Mac²⁴.

RESULTS

During the study period, a total 886 suicide attempts fulfilling inclusion criteria received medical assistance at La Paz University Hospital. The majority of them corresponded with females (68.2%). Table 1 summarizes the demographic characteristics of the study population, divided by study year.

Time between discharge and the first outpatient visit

Studying the distribution of the intervals of time between hospital discharge and first outpatient visit within 30 days, we found that year 2012's median±standard deviation 8.5±7.6 days were reduced, after the implementation of the program, to 6±7.3 in 2013 (p=0.03). We found an inverse correlation between study year and time between discharge

Table 1	Demographic characteristics and distribution of cases per study year			
	N	Age P50 (DS)	Men N (%)	Women N (%)
2012	199	42.66 (14.59)	53 (26.6%)	146 (73.4%)
2013	242	42.85 (17.46)	82 (33.9%)	160 (66.1%)
2014	265	39.08 (15.89)	76 (28.7%)	189 (71.3%)
2015	180	39.86 (15.93)	71 (39.4%)	109 (60.6%)
2012-15	886		282 (31.8%)	604 (68.2%)

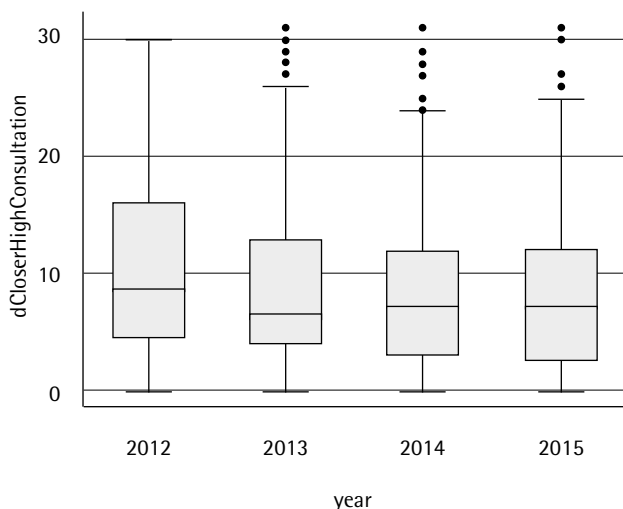


Figure 1 Time between discharge and first outpatient visit, within a maximum 1-month follow-up, per study year. Results in median \pm standard deviation are $P50 \pm SD$ 2012: 8.5 ± 7.57 ; 2013: 6 ± 7.31 ; 2014: 7 ± 6.91 ; 2015: 7 ± 6.54 ; $p=0.03$

and first visit, indicating a progressive increase in the program's real uptake ($R=-0.11$; $p<0.001$). Figure 1 represents this association. Table 2 displays the percentage of cases who were compliant with the program's main goal – having a consultation within 7 days, per study year. It also features the proportion of cases with no outpatient consultation. Given that a longer follow-up period increases the odds of having at least one visit after the index suicide attempt, this variable increased slightly as the study advanced.

Proportion of suicide reattempts, attempt rate per person-year and time between attempts

The distribution of suicide attempts per year was as follows: 199 cases in 2012, 242 cases in 2013, 265 cases in 2014, and 180 cases in 2015. Figure 2 shows the evolution in the proportion of attempts that corresponds to reattempts, a figure that decreased every study year. Figure 3 represents the evolution of the attempt rate per person-year throughout the study period. The rate decreased from 1.20 attempts in 2012 to 1.08 attempts in 2015 ($p=0.01$). Figure 4 shows the distribution of the intervals of time to reattempt, within

Table 2 Percentage of suicide attempts with time to first outpatient visit following discharge \leq or $>$ 7 days ($p=0.002$) and percentage of cases with no outpatient follow-up ($p<0.001$)

	Total	Follow-up ≤ 7 days	Follow-up > 7 days	No follow-up
2012	197	63 (32%)	134 (68%)	1%
2013	231	112 (48.5%)	119 (51.5%)	4.5%
2014	242	110 (45.5%)	132 (54.5%)	8.7%
2015	160	77 (48.1%)	83 (51.9%)	11.1%
Total	830	362 (43.6%)	468 (56.4%)	

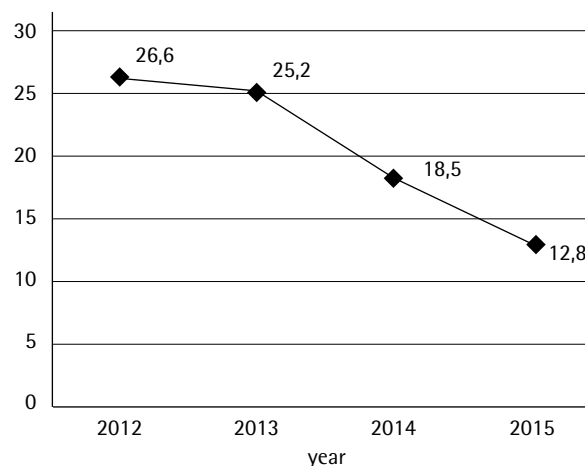


Figure 2 Percentage of suicide attempts that correspond to a reattempt per study year. $p=0.002$

a maximum 1-year follow-up, per study year: time between attempts progressively increased as the study advanced.

DISCUSSION

This retrospective study analyzed the degree of implementation and fulfillment of the ARSUIIC Suicide Risk Care Program, as well as its effectiveness. Our results show that, after ARSUIIC was implanted, the median time wait between a suicide attempt and the first outpatient follow-up was reduced from 8.5 to 6 days, and then it stabilized in 7

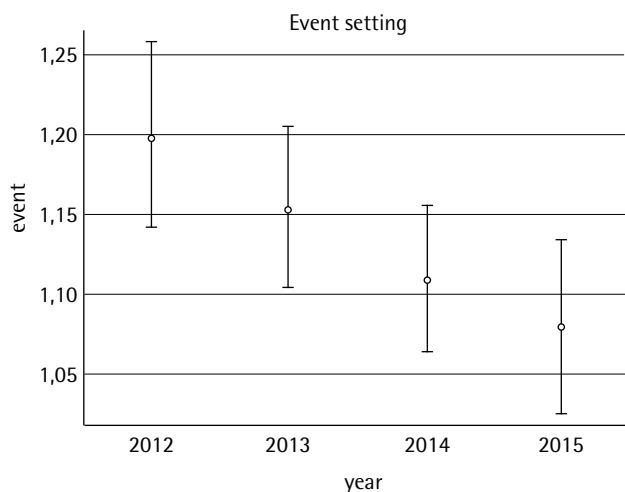


Figure 3 | *Suicide attempt rate per person-year. The difference between the logarithms of the rates 2012-2015 is statistically significant at an adjusted p-value level=0.017*

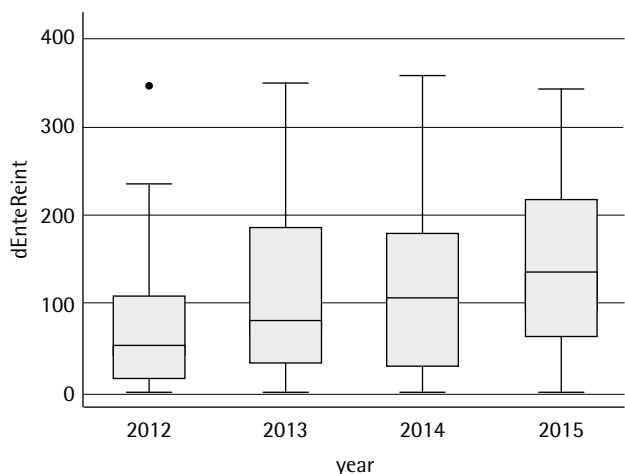


Figure 4 | *Time between hospital discharge following a suicide attempt and a subsequent suicide attempt, within a maximum 1-year follow-up, per study year. p=0.01*

days – the exact maximum that the program allows for. Moreover, the proportion of suicide attempts seen at the ED that correspond to reattempts decreased, and time between attempts in patients with multiple attempts increased. This is the first study to evaluate this program,

adopted in all hospitals across the Autonomous Community of Madrid since 2013.

Since the establishment of the program, a number of voices have rightfully pointed out the need for an evaluation of its results²⁵. In fact, implementing suicide prevention programs that are innovative and effective, and evaluating such programs with observational designs in real-world settings, are two global priorities²⁶. According to our results, median time to follow-up, considering only the first 30 days after discharge, has decreased until becoming compliant with the study's objectives. In addition, our study shows high adherence to follow-ups after suicide attempting – over 88% patients were seen at a CMHC at some point, following discharge. Notwithstanding, there is a marked proportion of patients who do not turn up to these outpatient visits within the maximum 7 days established in the program. During the study period, this proportion has lowered from 68% to roughly 50%. The figure is in keeping with a study from Barcelona, where up to 50% did not comply with a suicide risk reduction protocol based on telephone calls²⁷. Hence, while central tendency indicators suggest that ARSUIIC's goals have been fulfilled, there seem to exist substantial between-subject differences in effective access to care. The marked increase of absolute suicide attempts we observed between 2012 and 2014 is in line with trends reported elsewhere¹². Our ecological assessment of the program's effectiveness is promising: the proportion of attempts corresponding to reattempts and the suicide attempt rate per person-year have decreased every year since the program was implemented.

Our study includes several limitations that may somewhat affect its validity, and the applicability of our results. First, a proportion of all patients seen at the ED was under long-term treatment in a different catchment area, indicating the possibility that some suicide attempts pertaining to our studied area were, in turn, seen at other EDs, and are not included among our study population. Other authors, from comparable healthcare settings²⁸, maintain that, in Spain, most attempts are derived to the correspondent catchment area's ED. Overall, Madrid's healthcare planning has not suffered major changes during the study period, and we consider unlikely the possibility that this limitation affects between-study year differences. Thus, we believe that our findings are valid. Second, due to technical and ethical limitations, our effectiveness assessment is based on suicide reattempt, rather than death by suicide, as the measure of effect. Most authors agree that suicide attempt, as a relatively frequent event that can be registered in the clinical setting, is a useful proxy for death by suicide, an infrequent and difficult-to-detect outcome^{7-9,29}. Notwithstanding, other studies have reported profile differences between people who attempt suicide and those who die by suicide³⁰, and we consider that including suicide as an outcome should be a

priority in future assessments of the program. Last, our study uses an ecological and historical design to evaluate the program's effectiveness, two characteristics that limit our ability to draw causal inferences. The retrospective design increases the possibility of a potential undetected historical artifact affecting our results. For example, some authors have reported an association between the 2000s decade's economic downturn and suicide rates in Europe³¹. The ecological approach somewhat limits our study's applicability to the clinical practice, in terms of individual-level decision-making.

Our study's main strength is its naturalistic character that allows for the assessment of a recently implemented intervention in unselected patients. There is a growing demand for pragmatic intervention studies for comparative effectiveness research that favor the generation of external rather than internal validity and expedite the implementation of evidence-based programs³². The age and gender distribution of our study population are in line with those observed in comparable settings²⁷. We believe that our implementation estimates can be generalized to the rest of the Autonomous Community of Madrid, and that the effectiveness estimates are valid for other universal coverage healthcare systems. In addition, evidence suggests that, just as other subpopulations of patients under mental healthcare, people who attempt suicide have lower rates of adherence to outpatient care, as well as other inequities in access to care, than the general population^{20,33}. Hence, hospital contexts such as the ED are an opportunity to enhance their access to effective interventions^{20,33}. Our study contributes with novel information to the field of hospital-initiated interventions for suicide prevention in high-risk individuals. Last, the ecological approach to estimating the program's effectiveness makes our results especially useful for decision-making at the healthcare policy and management level. Although most clinical studies opt for an individual-level approach, it should be noted that suicide is, by definition, a complex problem that requires the assessment of ecological-level factors and how these interact with individual-level ones^{12,34}.

Further research is needed for a deeper understanding of the ARSUIIC Suicide Risk Care Program. Clarification of the barriers and facilitators that suicidal individuals face in the process of accessing the program is a priority, in order to reduce access inequality. Also, building on other authors' findings that similar, early contact enhancement programs might not be effective in the long-run³⁵, future repetitions of this evaluation will be required. Last, Lopez-Castroman and colleagues have pointed out that most suicides take place in low and middle income countries, while research is mainly conducted in high income countries³⁶. Direct comparisons to programs deployed in the same and other contexts will allow for the identification of common components, to estimate if the program is adaptable and scalable³⁷.

AUTHORS' CONTRIBUTION

- Idea and design: EJ, GMA, ER, PS, BRV, MBO.
- Data collection, analysis, interpretation: EJ, GMA, ER, PS.
- Manuscript writing: EJ, GMA, ER, PS.
- Manuscript review with important intellectual insights: CD, BRV, MBO.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest in regarding this article.

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Implementación de un programa de prevención del riesgo de suicidio en la Comunidad Autónoma de Madrid. La experiencia ARSUIC

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* Contribución idéntica (co-primeros autores)

Introducción. Este estudio evalúa el grado de cumplimiento y efectividad del programa ARSUIC de Atención al Riesgo Suicida, cuyo objetivo es reducir el riesgo posterior al intento de suicidio facilitando una cita ambulatoria de alta prioridad después del alta hospitalaria.

Metodología. Estudio retrospectivo de base hospitalaria conducido, entre 2012 y 2015, en todos los casos de intento de suicidio atendidos en la red de recursos de psiquiatría del Hospital Universitario La Paz. Se obtienen estimadores del tiempo hasta la primera consulta después del alta, de la proporción de citas que cumple el objetivo del programa de ser atendidos en un máximo de 7 días, de la tasa de intento de suicidio y del porcentaje de intentos que corresponde con un reintento, en cada año de estudio.

Resultados. Después de la implementación del programa, la mediana de tiempo entre el alta y la primera consulta baja de 8,5 a 6 días y el porcentaje de citas que cumplen el objetivo aumenta de 32 a 48,5%. Entre 2012 y 2015, la tasa de intentos de suicidio por paciente y año se reduce de 1,20 a 1,08, y el porcentaje de intentos que corresponde con reintentos de 26,6 a 12,8%.

Conclusión. La implementación del Programa ARSUIC ha reducido el tiempo entre el alta después de un intento de suicidio y la primera cita ambulatoria. Han disminuido los intentos de suicidio debidos a reintentos y la tasa de intentos por paciente y año. El porcentaje de cumplimiento menor al 50% sugiere diferencias interindividuales en el acceso efectivo al programa.

Palabras clave: Suicidio, Salud mental, Evaluación de programas, Implementación

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Implementation of a suicide risk prevention program in the Autonomous Community of Madrid. The ARSUIC experience

Introduction. This study evaluates the degree of compliance and effectiveness of the ARSUIC Suicide Risk Care Program. ARSUIC seeks to reduce the relapse risk that follows a suicide attempt by scheduling a high priority outpatient visit following hospital discharge.

Method. Hospital-based retrospective study conducted between years 2012 and 2015. We included every suicide attempt treated at the La Paz University Hospital's mental healthcare resources network. We estimated the time between hospital discharge and the first outpatient visit; the proportion of visits that fulfill the program's objective – a follow-up within a maximum of 7 days; the suicide attempt rate; and the percentage of attempts corresponding to relapses, by study year.

Results. After program deployment, median time between discharge and the first visit decreased from 8.5 to 6 days, and the percentage of visits that fulfill the program's objective increased from 32 to 48.5%. Between years 2012 and 2015, the suicide attempt rate per person and year decreased from 1.20 to 1.08 and the proportion of attempts corresponding to relapses from 26.6% to 12.8%.

Conclusion. Implementing the ARSUIC Program lowered the time between discharge and the first outpatient visit following a suicide attempt. The proportion of suicide attempts due to relapses and the suicide attempt rate per person decreased progressively. The program fulfillment proportion was under 50%, suggesting between-user differences regarding their effective access to the program.

Key words: Suicide, Mental health, Program evaluation, Implementation

INTRODUCCIÓN

Casi un millón de personas mueren anualmente por suicidio¹, la segunda causa de muerte más frecuente entre los jóvenes². En España, supone la primera causa de muerte externa, con una tasa anual que varía entre 11,88 suicidios por 100.000 personas en hombres y 4,05 en mujeres³. Los factores de riesgo del suicidio consumado interactúan en complejas redes jerárquicas^{4,5}. Entre ellos, el antecedente personal de intento de suicidio destaca como principal marcador clínico de riesgo de reintento y de suicidio consumado⁶. Se estima que un intento previo aumenta el riesgo de muerte por suicidio 30 veces, y lo antecede en la mitad de los casos⁷⁻⁹. Además, el intento de suicidio, una entidad hasta 30 veces más frecuente que el suicidio consumado¹⁰, constituye un problema clínico en sí mismo, con enormes costes directos e indirectos asociados y una incidencia en progresivo aumento en todo el mundo^{11,12}.

La prevención del suicidio se puede ejercer en diferentes niveles de intervención¹³. En el poblacional, varias medidas se han mostrado protectoras: en general, están orientadas a limitar el acceso a métodos potencialmente mortales. Algunos ejemplos incluyen reducir el contenido de las cajas de fármacos utilizados en sobredosis, como paracetamol o benzodiazepinas¹⁴, o dificultar el paso a "puntos calientes" de suicidio por precipitación¹⁵. La prevención individual del suicidio se ejerce a través de intervenciones clínicas para las personas con riesgo elevado. Se considera que el medio sanitario es adecuado para la detección del riesgo porque hasta el 45% de los sujetos que consuman el suicidio ha acudido a una consulta médica durante el mes previo¹⁶. Entre los pacientes con riesgo, destacan los que han tenido un intento de suicidio¹⁷, en especial durante el periodo inmediatamente posterior al alta, que asocia una extraordinaria vulnerabilidad al reintento¹¹. La mejor evidencia científica corresponde a estrategias de mantenimiento de contacto con el individuo en alto riesgo de suicidio a través de los llamados "gatekeepers", personas accesibles en momentos de crisis¹⁸. Un reciente metaanálisis de ensayos clínicos encontró que el WHO-BIC (*Brief Intervention and Contact*), un programa que potencia el contacto entre el personal clínico y el sujeto, es efectivo a la hora de reducir la tasa de repetición del intento de suicidio y el suicidio consumado¹⁹. En el mismo metaanálisis, las intervenciones psicoterapéuticas regladas no mostraron resultados positivos. El ensayo clínico pragmático ED-SAFE, conducido en Estados Unidos, concluyó que una intervención iniciada a nivel de urgencias hospitalarias, dirigida a clarificar los recursos en caso de crisis, era efectiva en la reducción de nuevos intentos y suicidios consumados²⁰.

En la Comunidad Autónoma de Madrid, el Plan Estratégico de Salud Mental para 2010-2014 señaló el riesgo de suicidio como una línea de trabajo fundamental, y marcó como objetivos la vigilancia epidemiológica del suicidio, el

desarrollo de un abordaje clínico normalizado para su prevención y el fomento de la investigación sobre las conductas suicidas²¹. Específicamente, se desarrolló el programa de Atención al Riesgo Suicida (ARSUIC), por el que se prioriza la atención a sujetos que han sufrido intentos de suicidio, con el objetivo de reducir el riesgo de nuevos intentos y del suicidio consumado. Aunque está implantado de forma general en la Comunidad Autónoma de Madrid desde 2013, no se han publicado sus resultados. El objetivo de este estudio es evaluar el programa ARSUIC con estimadores de implementación, cumplimiento y efectividad.

METODOLOGÍA

Diseño del estudio, contexto y sujetos

Estudio observacional retrospectivo de base hospitalaria. El Hospital Universitario La Paz (HULP) atiende a un área sanitaria de 525.501 personas en el norte de Madrid. La atención a los pacientes con necesidades psiquiátricas se realiza de manera articulada entre una variedad de recursos intra y extrahospitalarios, entre los que destacan el Servicio de Urgencias (SU), la Unidad de Hospitalización Breve Psiquiátrica (UHB) y los Centros de Salud Mental Comunitaria (CSM). Entre el 1 de enero de 2012 y el 31 de diciembre de 2015, se atendieron 1.633 urgencias hospitalarias debidas a intento de suicidio. Todos ellos recibieron valoración psiquiátrica antes del alta hospitalaria. Los pacientes atendidos en el SU pueden recibir el alta hospitalaria en la propia sala de urgencias. En caso de que el daño requiera ingreso para tratamiento médico, un psiquiatra (de Interconsulta y Enlace) evaluará al paciente una vez estabilizado. Por último, si el psiquiatra responsable considera que el riesgo de suicidio sigue siendo elevado, se puede realizar un ingreso en la UHB. Incluimos en el estudio a todos los sujetos que hubieran realizado un intento de suicidio, independientemente del dispositivo hospitalario desde el que hubiera sido dado de alta. En el contexto de la urgencia hospitalaria, se considera intento de suicidio cualquier acto autolesivo con al menos alguna intención de morir como resultado. Por lo tanto, no se incluyeron pacientes con ideación de suicidio que no hubiesen cometido ningún acto. Asimismo, y debido al objetivo del estudio de valorar el grado de cumplimiento del programa al alta en el propio área sanitaria, se excluyeron de la muestra los sujetos pertenecientes a otras áreas sanitarias, generalmente derivados a su correspondiente SU, cuyo seguimiento al alta e ingreso se realizarían en centros no pertenecientes a la red del HULP, así como aquellos que, perteneciendo al área sanitaria estudiado, ingresaron en otras UHB debido a falta de disponibilidad de camas o a su preferencia personal. El estudio cumple con la declaración de Helsinki

y cuenta con la autorización del Comité Ético de Investigación Clínica (CEIC) del HULP.

El programa de Atención al Riesgo Suicida (ARSUIC)

ARSUIC trata de asegurar una atención especializada prioritaria para los sujetos que han sufrido un intento de suicidio, potenciando el contacto con los profesionales de salud mental a lo largo de los primeros días posteriores al intento. Se implementó durante el último trimestre del año 2012. En el mismo periodo, las citas médicas preferentes en la Comunidad de Madrid tardaban en torno a los 19 días²². La principal medida de ARSUIC se basa en citar a todos los sujetos incluidos, con un psiquiatra ambulatorio sin especial entrenamiento en la prevención del suicidio, en un máximo de 7 días después del alta hospitalaria. Posteriormente, cada paciente continúa el tratamiento habitual con citas periódicas. Por lo tanto, no incluye más mantenimiento de contacto o intervención farmacológica o terapéutica más allá de la reducción del tiempo hasta la primera cita. La cita se organiza desde el propio hospital (SU, Interconsulta o UHB), y el psiquiatra responsable del alta hospitalaria la especifica en el informe.

VARIABLES ESTUDIADAS

La información relativa a las fechas de ingreso y alta se obtuvo de los registros informatizados hospitalarios que se rellenan previamente a cualquier alta hospitalaria (SU, Interconsulta, UHB). Los mismos registros contienen algunas variables sociodemográficas complementarias: (sexo, edad) y si el intento de suicidio es el primero o un reintento. La información relativa a la primera cita ambulatoria posterior al alta, y de la asistencia de cada paciente a la misma, se obtuvo de los registros informatizados de los CSM. Para valorar la implementación del programa estudiado, se consideraron los tiempos entre el alta hospitalaria y la primera cita en CSM durante los 30 días siguientes. De esta forma, evitamos que otras citas más alejadas, sin relación con el alta hospitalaria, sesguen los resultados a favor de los últimos casos registrados, que tienen menos tiempo de seguimiento. Se estudió el tiempo hasta la consulta como variable continua y, asimismo, como una variable dicotómica de implementación del programa (porcentaje de sujetos que acuden a consulta en un máximo de 7 días). Además, se computó el porcentaje de sujetos que no llegó a consultar después del intento de suicidio. A partir de las fechas de ingreso y alta hospitalarios recogidas, en los sujetos que sufrieron más de un intento de suicidio durante el tiempo de estudio, se calculó el tiempo entre intentos. Para valorar la efectividad del programa, se obtuvieron estimadores del tiempo entre intentos con un máximo de seguimiento de

un año, así como de la tasa de intento por persona-año en cada año de estudio.

ANÁLISIS ESTADÍSTICO

Se calcularon estadísticos descriptivos de las variables sociodemográficas, que se expresan en forma de porcentaje (cualitativas) y mediana±desviación estándar (cuantitativas). A continuación, se obtuvieron los estimadores del tiempo hasta la primera consulta, el tiempo entre diferentes intentos de suicidio y la tasa de intento por persona-año. Comprobamos que las variables cuantitativas son paramétricas con el test de Kolmogorov-Smirnoff, valoramos la tendencia temporal de las mismas a través de coeficientes R de Pearson y contrastamos las diferencias entre antes y después de la implementación del programa con test T de Student para muestras apareadas. Por último, estudiamos las tendencias temporales en la tasa de intento de suicidio por persona-año, empleando un modelo de regresión lineal generalizado (GLM). Las comparaciones interanuales de logaritmos de tasas se ajustaron por el método de Bonferroni para comparaciones múltiples. Los análisis se realizaron con el paquete estadístico SPSS v.22 para Windows²³ y con la colaboración del Equipo de Bioestadística del HULP; los gráficos se programaron en el paquete Stata v.13 para Mac²⁴.

RESULTADOS

En el periodo de tiempo de estudio, un total de 886 casos de intento de suicidio que cumplieran con los criterios de inclusión fueron atendidos en HULP. La mayor parte de intentos de suicidio se correspondió con mujeres (68,2%). La tabla 1 resume las características demográficas de los casos, divididas por año de estudio.

Tabla 1	Características demográficas y distribución de casos por año de estudio			
	N	Edad P50 (DS)	Hombres N (%)	Mujeres N (%)
2012	199	42,66 (14,59)	53 (26,6%)	146 (73,4%)
2013	242	42,85 (17,46)	82 (33,9%)	160 (66,1%)
2014	265	39,08 (15,89)	76 (28,7%)	189 (71,3%)
2015	180	39,86 (15,93)	71 (39,4%)	109 (60,6%)
2012-15	886		282 (31,8%)	604 (68,2%)

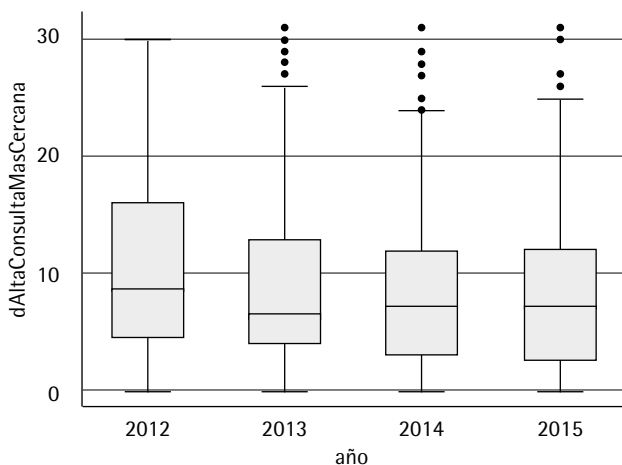


Figura 1 Distribución del tiempo entre el alta hospitalaria y la primera consulta ambulatoria, durante un máximo de 1 mes de seguimiento, por año de estudio. Los resultados en mediana de días \pm desviación estándar son P50 \pm SD 2012: 8,5 \pm 7,57; 2013: 6 \pm 7,31; 2014: 7 \pm 6,91; 2015: 7 \pm 6,54; $p=0,03$.

Tiempo entre el alta y la consulta ambulatoria más cercana

Estudiando la distribución del tiempo hasta la primera consulta dentro de los 30 días posteriores al alta, obtuvimos que de una mediana \pm desviación estándar de 8,5 \pm 7,6 días en 2012, se pasó a 6 \pm 7,3 después de implementar el programa, en 2013 ($p=0,03$). La correlación entre los sucesivos años de estudio y el tiempo hasta la primera consulta fue inversa, indicando un aumento progresivo en la implementación real del programa ($R=-0,11$; $p<0,001$). La figura 1 representa la distribución del tiempo hasta la consulta por año de estudio. La tabla 2 muestra el porcentaje de casos que cumplieron con el objetivo de acudir a consulta en un tiempo menor o igual a 7 días por año de estudio. También incluye la proporción de casos que no llegaron a consultar ambulatoriamente. Como un seguimiento más largo aumenta la probabilidad de tener alguna consulta, esta variable aumentó conforme avanzaba el estudio.

Porcentaje de reintentos de suicidio, tasa de intentos por persona-año y tiempo entre intentos

La distribución de intentos de suicidio atendidos fue la siguiente: 199 casos en 2012, 242 casos en 2013, 265 casos

Tabla 2	Porcentaje de casos de intento de suicidio con tiempo hasta la consulta posterior al alta hospitalaria \leq o $>$ a 7 días ($p=0,002$) y porcentaje de casos que no se siguen de consulta ambulatoria ($p<0,001$)			
	Total	Consulta ≤ 7 días	Consulta > 7 días	No consulta
2012	197	63 (32%)	134 (68%)	1%
2013	231	112 (48,5%)	119 (51,5%)	4,5%
2014	242	110 (45,5%)	132 (54,5%)	8,7%
2015	160	77 (48,1%)	83 (51,9%)	11,1%
Total	830	362 (43,6%)	468 (56,4%)	

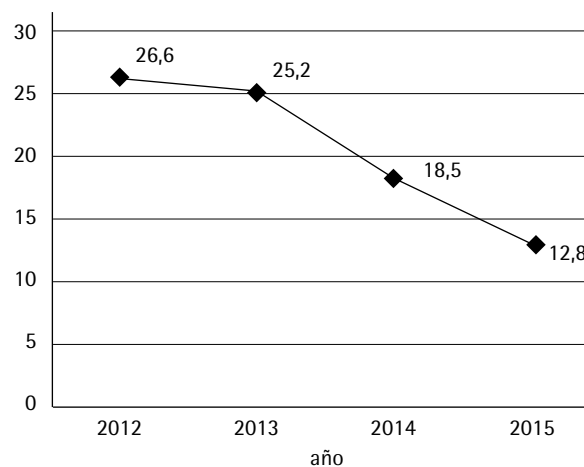


Figura 2 Porcentaje de intentos de suicidio que corresponden a un reintento, por año de estudio. $p=0,002$

en 2014 y 180 casos en 2015. La figura 2 muestra la evolución del porcentaje de intentos de suicidio que se debe a reintentos. Cada año de estudio, este porcentaje se redujo. La figura 3 representa la evolución de la tasa de intento de suicidio por paciente-año a lo largo del estudio. La tasa se redujo desde 1,20 intentos en 2012 a 1,08 en 2015 ($p=0,01$). La figura 4 muestra la distribución del tiempo hasta el reintento, durante un seguimiento máximo de un año, por año de estudio. Se puede apreciar un aumento del tiempo entre intentos conforme el estudio avanza.

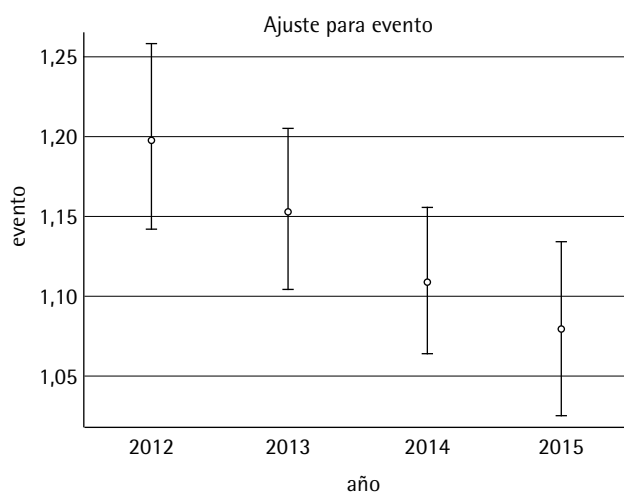


Figura 3

Tasa de intento de suicidio por persona-año. Diferencia entre los logaritmos de las tasas de 2012 y 2015 significativa, p ajustada=0,017

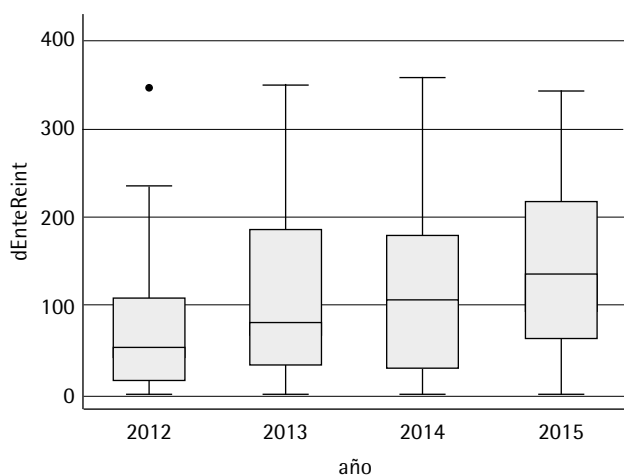


Figura 4

Distribución del tiempo entre el alta hospitalaria y la siguiente atención por un reintento de suicidio durante un tiempo máximo de seguimiento de un año, por año de estudio. $p=0,01$

CONCLUSIONES

En este estudio retrospectivo se analizaron el grado de implementación y cumplimiento de objetivos y la efectividad del programa ARSUIC de Atención al Riesgo Suicida. Los resultados muestran que el tiempo mediano entre el alta hospitalaria después de un intento de suicidio y la primera consulta ambulatoria se ha reducido, con la introducción

de ARSUIC, de 8,5 a 6 días, para pasar a estabilizarse en los 7 días máximos que el programa establece como objetivo. Asimismo, el porcentaje de intentos de suicidio atendidos en urgencias que se corresponden con reintentos ha descendido y el tiempo entre diferentes intentos de un mismo paciente ha aumentado. Se trata del primer estudio que evalúa este programa, adoptado de forma generalizada en todos los hospitales de la Comunidad Autónoma de Madrid desde 2013.

Desde la puesta en marcha del programa ARSUIC, algunas voces han señalado la necesidad de valorar sus resultados²⁵. De hecho, programas de prevención del riesgo de suicidio efectivos e innovadores, y evaluar dichos programas con diseños observacionales en población real han sido identificados como prioridad a nivel global²⁶. De acuerdo con nuestros resultados, el tiempo mediano hasta la primera consulta, después del alta hospitalaria, y tomando únicamente los primeros 30 días de seguimiento, se ha reducido hasta cumplir con el objetivo del programa. Asimismo, nuestro estudio muestra un elevado porcentaje de seguimiento posterior al intento de suicidio cuando se consideran las citas sin límite de tiempo, con una adherencia por encima del 88%. No obstante, existe un llamativo porcentaje de pacientes que no acuden a la consulta ambulatoria en el tiempo marcado por el programa, si bien se ha reducido de un 68 a un 50% aproximadamente. Un estudio conducido en Barcelona mostró resultados comparables, con un 50% de pacientes que no cumplían con un protocolo de reducción del riesgo de suicidio basado en llamadas telefónicas²⁷. Por lo tanto, si bien en términos de medidas de tendencia central el objetivo del programa se ha cumplido, parece que existen diferencias interindividuales en el acceso efectivo al mismo. El marcado aumento progresivo de los intentos de suicidio, en términos absolutos, observado en nuestro estudio entre 2012 y 2014, se asimila a las tendencias observadas en otros centros en el mundo¹². La valoración ecológica de la efectividad muestra resultados alentadores: el porcentaje de intentos de suicidio que se deben a reintentos y la tasa de intento de suicidio por paciente-año han ido reduciéndose cada año desde la implementación del programa.

Nuestro estudio incluye algunas limitaciones que modulan la validez y aplicabilidad de sus resultados. En primer lugar, un porcentaje de los sujetos atendidos en urgencias hacía su seguimiento en otro centro sanitario, lo que sugiere la posibilidad de que algunos intentos de suicidio que corresponden con el área estudiada, pero fueran atendidos en otros hospitales, no estén incluidos en nuestros resultados. Otros autores de áreas sanitarias comparables²⁸ sostienen que, en España, la mayor parte de intentos de suicidio son derivados a sus centros de referencia. No obstante, y dado que la ordenación de la atención especializada en la Comunidad Autónoma de Madrid no ha cambiado durante el periodo de estudio, consideramos poco probable que esta li-

mitación altere diferencialmente los estimadores entre años de estudio. Por tanto, consideramos que las diferencias encontradas son válidas. En segundo lugar, nuestra valoración de la efectividad ha utilizado como medida de resultado el reintento de suicidio, y no el suicidio consumado, por razones técnicas y de protección de datos individuales. La mayor parte de autores están de acuerdo en la utilidad del intento de suicidio, un evento frecuente, como variable instrumental del suicidio consumado, menos frecuente y más difícil de detectar^{7-9,29}. No obstante, se han notificado diferencias entre los perfiles de las personas que intentan el suicidio y las que lo consuman³⁰, y consideramos que incluir el suicidio consumado será necesario en estudios futuros. Por último, nuestro estudio utiliza un diseño histórico y ecológico para valorar la efectividad del programa, lo que reduce su capacidad para realizar inferencia causal. El planteamiento retrospectivo aumenta la posibilidad de un posible artefacto histórico no identificado que afecte a las diferencias encontradas. Por ejemplo, algunos autores han encontrado asociación entre la crisis financiera de la década de los 2000 y la incidencia de suicidios³¹. El abordaje ecológico limita nuestra capacidad para dar respuestas válidas para la práctica clínica.

La principal fortaleza de nuestro estudio es su carácter naturalístico, que permite valorar una intervención de reciente implementación en pacientes poco seleccionados. Existe una creciente demanda de estudios de intervención pragmáticos, que favorezcan la generación de validez externa por encima de la interna, y que aceleren la implementación de intervenciones basadas en la evidencia³². La edad media y el sexo predominantemente femenino de nuestros pacientes se asemejan a los observados en otras muestras clínicas de ámbitos comparables²⁷. Consideramos que nuestros estimadores de implementación son generalizables al resto de la Comunidad Autónoma de Madrid, mientras que los de efectividad lo son a otros sistemas de atención sanitaria universales. Además, la evidencia sugiere que, al igual que otros pacientes en seguimiento en los servicios de salud mental, los sujetos que sufren intentos de suicidio tienen menores tasas de adherencia al seguimiento ambulatorio, así como otras inequidades en el acceso a los tratamientos disponibles^{20,33}. Por lo tanto, contextos hospitalarios como el servicio de urgencias son una oportunidad para facilitar su acceso a los tratamientos que han demostrado efectividad^{20,33}. Nuestro estudio contribuye con información novedosa al campo de las intervenciones para la prevención indicada de las conductas suicidas iniciadas en el medio hospitalario. Por último, el planteamiento ecológico del estudio de la efectividad confiere a nuestros resultados una utilidad especial para la toma de decisiones en política sanitaria y gestión de centros. Aunque la mayor parte de estudios con población clínica se centran en la perspectiva individual, conviene recordar que el suicidio es, por definición, un problema "complejo" que requiere valorar factores ecológicos y cómo interactúan con los individuales^{12,34}.

Se requieren más estudios que permitan entender con mayor profundidad el programa ARSUIC de Atención al Riesgo Suicida. Es prioritario clarificar qué barreras y facilitadores individuales determinan el acceso efectivo al programa, para poder reducir inequidades en el mismo. Además, y dado que algunos autores han puesto en duda la efectividad a largo plazo de programas similares³⁵, serán necesarias nuevas evaluaciones futuras. Por último, López-Castromán y cols. han señalado que la mayor parte de fallecimientos por suicidio tienen lugar en países de pequeño y mediano ingreso, mientras que la investigación al respecto se concentra en países desarrollados³⁶. La comparación directa con programas comparables implementados en el mismo y otros contextos permitirá identificar componentes comunes y estudiar su adaptabilidad y escalabilidad³⁷.

CONTRIBUCIÓN DE LOS AUTORES

- Concepción y diseño: EJ, GMA, ER, PS, BRV, MBO.
- Recogida de datos, análisis e interpretación: EJ, GMA, ER, PS.
- Escritura: EJ, GMA, ER, PS.
- Revisión crítica con importantes aportaciones intelectuales: CD, BRV, MBO.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflictos de interés en relación con el presente artículo.

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An Emergency Department-Initiated Intervention to Lower Relapse Risk after Attempted Suicide

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Objective: According to randomized trials, contact after a suicide attempt lowers relapse risk. However, effectiveness studies based on real clinical data can provide additional external validity.

Method: We conducted an observational study to determine if an emergency department (ED)-initiated intervention for suicide attempt risk reduction, consisting on scheduling a single added appointment within 7 days after discharge following a suicide attempt, can reduce the risk of relapse. The study included 1,775 patients who had been treated at a general hospital ED due to a suicide attempt. The principal outcome measure was ED return after a new attempt. We obtained Kaplan-Meier survival functions and used Cox proportional hazard regression models to estimate unadjusted and adjusted risks of relapse by treatment phase. Covariates included: age, gender, history of suicide attempts, history of psychiatric disorders, concurrent alcohol/drug abuse, number of attempts during follow-up, admission as an inpatient and family support.

Results: A total of 497 (22.5%) attempts were followed by a relapse. Subjects exposed to the studied intervention had a lower risk of relapse after a suicide attempt, with a 24% adjusted risk reduction estimate.

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The study protocol complies with the Declaration of Helsinki for Human Rights and has the approval of the Hospital Universitario La Paz's Ethical and Clinical Research Committee.

The data sets generated and analyzed during the current study are not publicly available, because restrictions apply to data from public general hospitals in the Community of Madrid. However, the corresponding author can ask for the Ethic's Committee permission for partial share under reasonable request.

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Conclusion: Our real-world results suggest that an additional early appointment, scheduled before discharging suicide attempters, reduces suicide reattempt risk.

Suicide is considered the second most frequent cause of death between 15 and 29 years of age and accounts for over 800,000 annual deaths worldwide (WHO, 2018). In Spain, annual incidence varies between 11.7 suicides per 100,000 people in men and 3.8 in women (INE, 2017). Main risk factors for accomplished suicide interact in complex hierarchical networks (O'Connor & Nock, 2014; Van Heeringen & Mann, 2014). Mental disorders are considered among the strongest predictors (Holmstrand, Bogren, Mattison, & Bradvik, 2015). For instance, suicide is 20 times more likely if a previous diagnosis of major depression is present. Suicide is also associated with bipolar disorder, drug and alcohol addiction disorders, and psychoses, as well as to a broad variety of social stressors, such as socioeconomic disadvantage and the lack of social support (Bertolote, Fleischmann, De Leo, & Wasserman, 2002). However, nonlethal suicidal behaviors are considered the most specific risk marker (Arias et al., 2016; Turecki & Brent, 2015). Some researchers find that these behaviors may involve almost 30 times more incidence of accomplished suicide (Finkelstein et al., 2015). Addressing suicidal behavior, therefore, offers a great opportunity to prevent future suicide attempts. Moreover, suicidal behaviors drive high direct medical costs (Czernin et al., 2012) and entail over \$93 billion in total burden per year, only in the United States (Shepard, Gurewich, Lwin, Reed, & Silverman, 2016).

Several prevention programs, aimed at different levels, have been established in order to reduce suicide and suicidal behaviors (Mann et al., 2005). At the individual level, the referral of high-risk individuals to general mental health services (Van der Feltz-Cornelis et al., 2011) and, more specifically, to programs directly addressing suicidal behaviors (Meerwijk et al., 2016) is effective. The first weeks following an attempted suicide entail an exceptionally high reattempt risk (Owens, Horrocks, & House, 2002; Parra-Urbe et al.,

2017). Accordingly, some high-risk case-management programs focus on enhancing patient engagement, favoring access to medical resources after discharge through strategies such as telephone calls or emergency-contact cards (Mann et al., 2005; McMain, Guimond, Barnhart, Habinski, & Streiner, 2017). Emergency departments (ED) can play a key role in such strategies: Suicide attempters treated at the ED frequently repeat self-harm during the following year (Olson, Wall, et al., 2017), and a single ED visit for self-harm increases future suicide risk nearly sixfold (Owens et al., 2002). In addition, suicidal ED patients have low rates of outpatient treatment engagement (Lizardi & Stanley, 2010; Shand et al., 2017). Hence, there is a growing interest in brief interventions initiated at the ED that can enhance retention and prevent suicidal crises (Arias et al., 2016). Results from a randomized trial (RCT) showed a 30% decrease in subsequent suicide attempts after an ED-based intervention consisting on a combination of suicide risk screening, discharge resources, and telephone calls (Miller et al., 2017). In clinical research, however, comparative effectiveness studies based on data from the real clinical practice can add external validity to the evidence provided by RCTs (Sherman et al., 2016).

In Spain, suicide rates have steadily increased throughout the last two decades (INE, 2017; Ruiz-Pérez & Olry de Labry-Lima, 2006). The Community of Madrid's Regional Office of Mental Health established suicidal behavior prevention as a priority in its 2010–2014 Mental Health Strategy. This implied to launch the Suicide Risk Attention Program. Its main purpose is to offer priority specialized care to those patients who have attempted suicide, in order to prevent potential relapses. The present study evaluates its clinical effectiveness at reducing the risk of relapse among patients discharged from the ED after a suicide attempt.

METHODS

Study Setting

The Spanish tax-funded National Health Service (NHS) provides universal access to medical care. The Community of Madrid's Health Council organizes its psychiatric care in 25 community-based catchment areas. Each area includes a general hospital and a network of in- and outpatient psychiatric care and rehabilitation resources. Most of the patients with psychiatric needs use this network, and they usually come from primary care. We conducted our study in a northern catchment area, with a total population of 525,500 persons by the beginning of the study.

Study Design and Subjects

We conducted an observational study. Between January 1, 2010, and December 31, 2015, every suicide attempt receiving medical and psychiatric attention at the ED entered the study, regardless of whether admission to a medical or psychiatric ward was indicated following ED discharge. In this particular ED, every subject in an emergency psychiatric need first undergoes general medical assessment and treatment and then receives psychiatric care. In addition, anybody presenting with suicide ideation or a suicide attempt has to be seen by a psychiatry consultant before hospital discharge. If medical damage due to the suicide attempt requires admission in a medical ward, a psychiatrist evaluates the patient once stabilized. If the psychiatrist considers that the relapse risk remains excessively high, voluntary or involuntary psychiatric admission can be indicated. We defined suicide attempt as any self-injurious act committed with at least some intent to die as a result. Therefore, we excluded patients exhibiting suicide ideation without suicidal behavior. Otherwise, every suicide attempt was admitted to the study and included in the analyses. We considered each attempt a unit of analysis given that the intervention was widely administered at

discharge, regardless of whether it was a first suicide attempt or a relapse. The study protocol complies with the Declaration of Helsinki for Human Rights and has the approval of the La Paz general hospital's Ethical and Clinical Research Committee. Data were anonymized before extracting sociodemographic and clinical information from patient records.

Intervention

The Suicide Risk Attention Program (ARSUIC, by its Spanish acronym) seeks to ensure a prioritized and specialized care for those individuals who have attempted suicide, fostering potential contacts with mental health workers during the more dangerous first days after the attempt. It was implemented across the Community of Madrid during the last trimester of 2012. Previously, priority specialized appointments could take up to 19 days (Madrid's Health Results Observatory, 2017). The program considers that every suicide attempter must have an appointment with a general psychiatrist with no specific suicide prevention training within the first 7 days after hospital discharge. Hence, it does not imply any specific contact maintenance strategy or therapeutic intervention other than scheduling a priority outpatient visit in the next 7 days. The date and time of the appointment are explained to the patient and indicated in the hospital discharge report by the ED psychiatrist or, if the patient has been admitted to the hospital, by the treating psychiatrist. Following the priority appointment, the patient continues the usual psychiatric care; no further follow-up contacts are used, and no specific materials are shared. No new staff has been hired to conduct the program; instead, every community psychiatrist should devote a number of weekly consultation hours to the program.

Variables and Outcomes

Information of prognostic interest was selected according to prior existing knowledge (Arias et al., 2016; Turecki & Brent,

2015). By protocol, an individual semi-structured interview is performed prior to hospital discharge and stored in computer databases for clinical purposes. In addition, we reviewed each subject's historical medical records to identify previous attempts and psychiatric diagnoses. Clinical variables included the following: personal history of psychiatric disorder, previous suicide attempts, concurrent alcohol or abuse drugs use, and hospital admission after the attempt. Sociodemographics considered age (continuous variable), and gender and family support after discharge (dichotomous variables). Additional dichotomous variables regarding psychiatric diagnoses in medical records were included, according to the presence or absence of ICD-10, chapter V, F10-69 diagnostic groups (mental and behavioral disorders due to psychoactive substance use; schizophrenia, schizotypal and delusional disorders; mood disorders; neurotic, stress-related and somatoform disorders; behavioral syndromes associated with physiological disturbances and physical factors; and disorders of adult personality and behavior) (ICD, 1992).

We defined the outcome of interest as being admitted to the emergency department due to a new suicide attempt (any self-injurious act committed with at least some intent to die) during the follow-up after a previous suicide attempt. If a recurrence happened during follow-up time, it was considered a relapse, and the time between attempts was measured. Time to the event of interest was obtained from hospital's records. Every attempt, and its follow-up time, was considered.

Data Analyses

Suicide attempts were divided according to whether they had happened in the 3 years prior to the program implementation, the "control period" (2010–2012), or the three-ones during the "intervention period" (2013–2015). Initially, we compared baseline clinical and sociodemographic correlates in both periods, using Student's *t* test for

differences in continuous variables and Pearson's chi-square test for those in categorical ones.

Then, we conducted a survival analysis. We censored those subjects who had not suffered the outcome of interest by the end of each period's follow-up. We obtained Kaplan–Meier estimates of the survival function, both for the whole study time and by periods. We tested the difference between periods using log-rank test. In order to estimate the intervention's influence in the risk of relapse, we conducted Cox proportional hazard regressions, obtaining crude and adjusted risk estimates (hazard ratio, HR). For the multivariate models, we retained those covariates remaining significant to the $p < .10$ level, utilizing an automatic method for their introduction, as well as those variables considered to be clinically relevant according to prior knowledge. Number of relapses during the follow-up was included as a continuous variable, in order to control its possible role as a source of confounding. Then, we estimated the number needed to treat (NNT) and its 95% CI from the multivariate model B, following widely accepted methods (Altman & Andersen, 1999). The fulfillment of proportional hazards assumption requirements was ascertained both through graphic methods and using Schoenfeld's test. Analyses were carried on Stata v13 software for Mac (StataCorp, 2013. College Station, TX, USA).

RESULTS

Clinical and Demographic Characteristics

We included data from 2,347 suicide attempts treated at the ED by a psychiatrist, between January 1, 2010, and December 31, 2015. "Control period" comprised 1,176 attempts, while "intervention period" included 1,171. Globally, 1,775 subjects attempted suicide. Figure 1 illustrates the attempt–reattempt distribution across the study subjects. Thirty-nine subjects were excluded due to computer-related data mistakes. The two major repeaters suffered 14

suicide attempts during the time of study. Table 1 shows baseline characteristics of the included cases, both for the whole study period and by treatment groups. In most cases, the subject was female (68.3%) and the mean age in years was 40.5. As for the most relevant risk factors, 73.9% had a personal history of at least one psychiatric disorder, 40.3% had a substance abuse disorder, and 48.4% had previously attempted suicide at least once. Most frequent psychiatric diagnoses were as follows: “Mental and behavioral disorders due to psychoactive substance use” (37.5%), “Neurotic, stress-related and somatoform disorders” (37.5%) and “Mood (affective) disorders” (39.4%). Comparing both groups showed that control period had a lower prevalence of family support (62.3% vs. 74.5%), a lower presence of concurrent alcohol/drug abuse (39.1% vs. 41.4%), and a higher percentage of inpatient admission after the suicide attempt (24.5% vs. 20.5%).

Follow-up and Relapse

A total 497 (21.2%) cases relapsed during follow-up. The intervention group had a lower incidence of relapse during follow-up (18.3% vs. 24.1%; $p < .01$). Curves obtained from Kaplan–Meier survival probability and multivariate-adjusted survivor functions are shown in Figure 2. Median follow-up was 434 days for the whole study, 394 for the control group, and 468 for the intervention group. Differences between control and intervention group’s survival probability estimates are statistically significant (log-rank test $p < .01$). Table 2 displays results from the adjusted and unadjusted Cox proportional hazard models. Univariate models showed an association between a higher risk of relapse and the following risk factors: personal history of psychiatric disorders, personal history of suicide attempts, and concurrent alcohol or drug abuse. The presence of social support was a protective factor. For the multivariate models, we retained those variables that were significant at the $p < .05$ level (multivariate model A), as well as those variables considered clinically relevant (multivariate model B). Results show that attempts followed by a scheduled priority appointment had a lower risk of relapse, with little difference between estimates from the unadjusted model, HR (95% CI) = 0.72(0.60–0.82), and the multivariate models, A, HR (95% CI) = 0.76 (0.62–0.93), and B, HR (95% CI) = 0.69 (0.54–0.87). The proportional hazards assumption was fulfilled (Schoenfeld’s residuals test $p = .30$; $p = .15$ and $p = .14$ for the univariate and multivariate models A and B, respectively). The NNT (95% CI) estimate obtained from the multivariate model B was 7.7 (4.5–20.0).

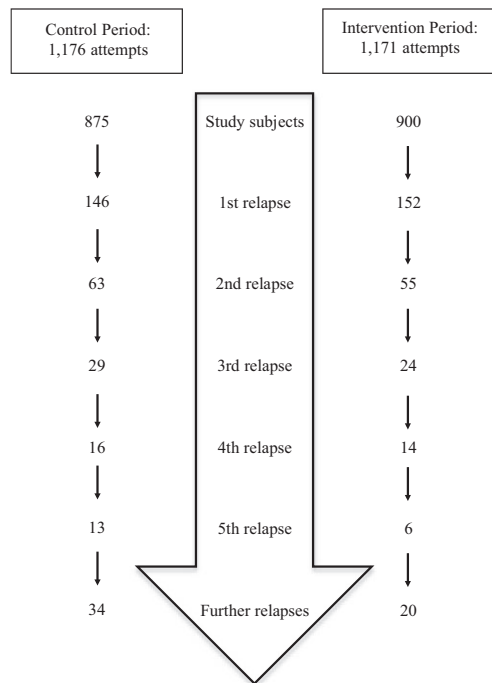


Figure 1. Distribution of repeated suicide attempts among subjects across study periods.

DISCUSSION

In this observational study, scheduling a priority outpatient psychiatry appointment lowered the risk of relapse among suicide attempters by up to 25% over a three-year follow-up. This is the first study to confirm

TABLE 1

Baseline Clinical and Sociodemographic Covariates of the 2,347 Episodes attempted by the 1,775 Study Subjects, Globally and Divided by Period of Treatment

		Total	Control period	Intervention period	<i>p</i>
Total study subjects	<i>N</i> (%)	1,775	875 (49.3)	900 (50.7)	
Total suicide attempts	<i>N</i> (%)	2,347	1,176 (50.1)	1,171 (49.9)	
Age in years	Mean (<i>SD</i>)	40.5 (16.7)	40.2 (16.3)	40.8 (17.0)	0.36
Female	<i>N</i> (%)	1,602 (68.3)	814 (69.2)	788 (67.3)	0.32
Personal history of a psychiatric disorder	<i>N</i> (%)	1,735 (73.9)	883 (75.1)	852 (72.7)	0.00
ICD-10 F10-19	<i>N</i> (%)	880 (37.5)	412 (35.5)	468 (40.0)	
ICD-10 F20-29	<i>N</i> (%)	162 (6.9)	98 (8.3)	64 (5.4)	
ICD-10 F30-39	<i>N</i> (%)	925 (39.4)	441 (37.5)	484 (41.0)	
ICD-10 F40-49	<i>N</i> (%)	880 (37.5)	416 (35.4)	464 (39.6)	
ICD-10 F50-59	<i>N</i> (%)	145 (6.2)	65 (5.5)	80 (6.8)	
ICD-10 F60-69	<i>N</i> (%)	401 (17.1)	194 (16.5)	207 (17.7)	
Personal history of suicide attempts	<i>N</i> (%)	1137 (48.4)	571 (48.6)	566 (48.3)	0.07
Concurrent alcohol/drug abuse	<i>N</i> (%)	945 (40.3)	460 (39.1)	485 (41.4)	0.00
Family support	<i>N</i> (%)	1,604 (68.3)	732 (62.3)	872 (74.5)	0.00
Admitted after ED discharge	<i>N</i> (%)	528 (22.5)	288 (24.5)	240 (20.5)	0.00

p-Values are obtained from Student's *t* test for the quantitative covariates and Pearson's chi-square test for the qualitative ones.

ED, emergency department; ICD-10, International Classification of Diseases 10th Revision; F10-19, mental and behavioral disorders due to psychoactive substance use; F20-29, schizophrenia, schizotypal and delusional disorders; F30-39, mood (affective) disorders; F40-48, neurotic, stress-related and somatoform disorders; F50-59, behavioral syndromes associated with physiological disturbances and physical factors; F60-69, disorders of adult personality and behavior.

the effectiveness of the ARSUC Suicide Risk Attention Program, a contact enhancement intervention, currently in use throughout the Community of Madrid, Spain. Because we stuck to a strictly naturalistic design and included data from the real clinical practice, recruiting all suicide attempt patients treated at the ED level with no exclusion criteria, the results likely capture the implemented program's true effectiveness. The effect estimates are consistent with those of other interventions aimed at contact maintenance (Zalsman et al., 2016), including studies conducted in other European countries (Cebriá et al., 2013; Reijas, Ferrer, González, & Iglesias, 2013), the United States (Miller et al., 2017), and several low- and middle-income countries (LMIC) (Riblet, Shiner, Young-Xu, & Watts, 2017). In keeping with the literature, risk factors for reattempts included a personal

history of previous suicide attempts, the presence of a diagnosed psychiatric disorder, female gender, and concurrent alcohol or drug abuse, while family support was a protective factor.

Emergencies because of attempted suicide have steadily increased throughout the last decades worldwide (Ting, Sullivan, Boudreaux, Miller, & Camargo, 2012; Zalsman et al., 2016), and their frequency typically peaks among the younger age groups (Canner, Giuliano, Selvarajah, Hammond, & Schneider, 2015). Our results contribute with relevant information regarding the effectiveness of ED-initiated outpatient preventive programs directed toward attempters, considered exceptionally high-risk individuals. Given that discharge after a suicide attempt entails a remarkably high risk of relapse, a majority of prevention strategies have focused

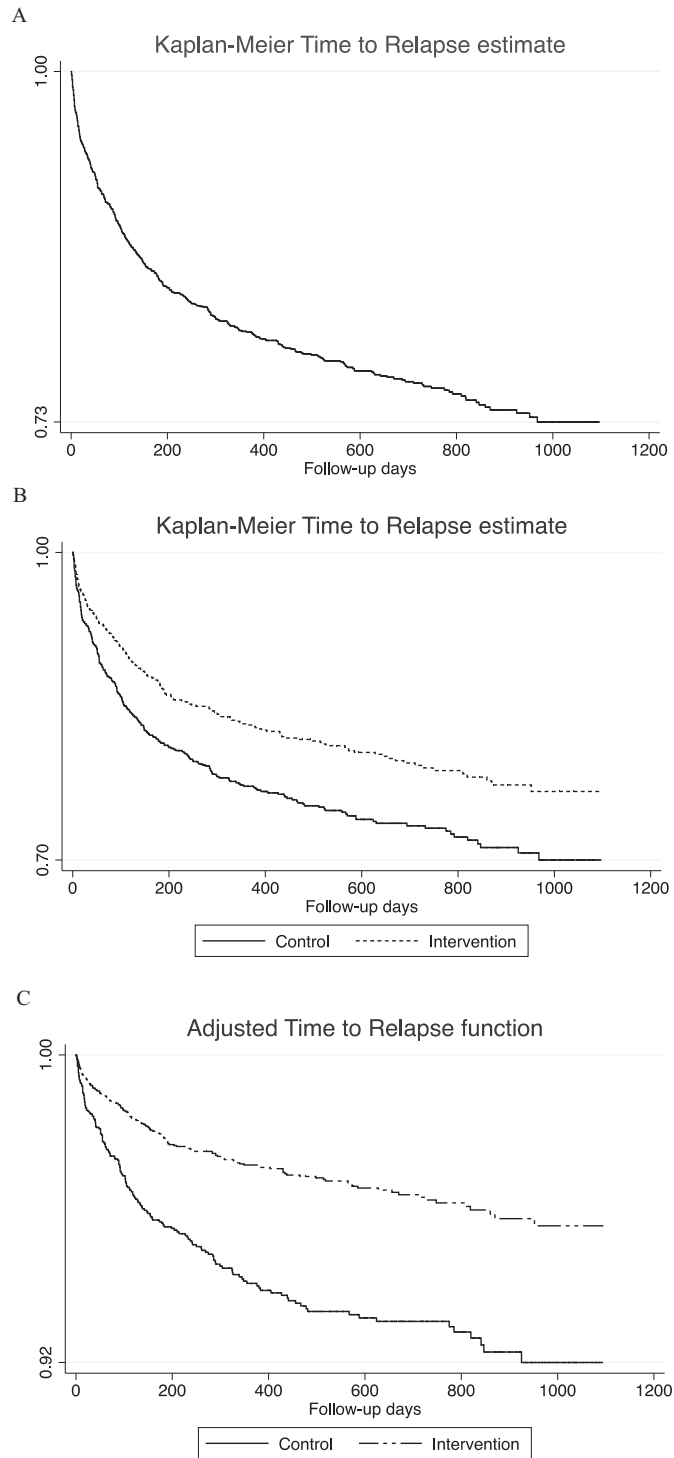


Figure 2. Kaplan–Meier survival function estimates. (A) Shows the graphic representation of time to relapse estimate including every suicide attempt recorded between 2010 and 2015. (B) Shows the graphic representation of time to relapse estimates divided by treatment period. (C) Adjusted survivor functions, following multivariate model (A). Differences shown are significant with a log-rank test's $p < 0.001$.

TABLE 2

Risk of relapse during the follow-up, derived from a Cox proportional hazard model including time to relapse as the outcome and the clinical and sociodemographic covariates as predictors

	Relapsed during follow-up N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	
			Model A	Model B
Control period (REF)	283 (24.1)	1	1	1
Intervention period	214 (18.3)	0.72 (0.60–0.82)	0.76 (0.62–0.93)	0.69 (0.54–0.87)
Female	609 (38.0)	1.17 (0.96–1.42)	1.30 (1.03–1.68)	1.30 (1.02–1.65)
Personal history of psychiatric disorder	757 (43.6)	3.21 (2.30–4.47)	1.99 (1.33–2.99)	2.03 (1.30–3.18)
Personal history of suicide attempts	627 (55.2)	2.71 (2.20–3.34)	2.29 (1.77–2.96)	2.32 (1.75–3.06)
Concurrent alcohol/drug abuse	468 (49.5)	1.77 (1.46–2.15)	1.55 (1.25–1.90)	1.58 (1.26–1.98)
Family support	640 (39.9)	0.64 (0.49–0.83)	0.74 (0.56–0.99)	0.66 (0.49–0.89)
Number of relapses	–	1.39 (1.36–1.42)	1.35 (1.31–1.39)	1.33 (1.29–1.37)
Admitted after ED discharge	248 (47.0)	1.14 (0.93–1.40)	–	1.20 (0.94–1.53)
Age in years	–	1.00 (0.99–1.00)	–	0.99 (0.99–1.00)

Control period is the reference. Multivariate model A retained those covariates associated with the $p \leq 0.05$ significant level. Model B included additional covariates, relevant according to the proposed causal frame.

in this period (Meerwijk et al., 2016; Milner, Carter, Pirkis, Robinson, & Spittal, 2015). Contact-enhancing programs, specifically directed at establishing brief contacts and maximizing access to clinical and social resources, are considered effective: Accordingly, a range of evidence-based contact maintenance programs including the use of letters, telephone calls, messages, or case management have been successfully developed, deployed, and scaled-up (Berrouiguet et al., 2014; Dekker, Vergouwen, Buster, & Honig, 2017; Vaiva et al., 2011). Recently, the WHO Brief Intervention and Contact (WHO BIC), a strategy searching to enhance contact after a suicide attempt, was the only intervention to significantly lower the risk of suicide in a recent meta-analysis of randomized control trials (RCT) including other therapeutic and pharmacologic strategies and a variety of different locales (Riblet et al., 2017). In the ED-Safe study, an RCT conducted in North American subjects, a brief ED-based intervention, consisting on postdischarge resources and telephone calls, significantly

decreased reattempts, with an incidence rate ratio (95% CI) of 0.72 (0.52–1.00) (Miller et al., 2017). However, studying suicide behaviors using experimental designs can be technically and ethically challenging, and a call has been made to conduct effectiveness and implementation studies on naturalistic settings, in order to obtain externally valid real-world data that can inform decision-makers (Sherman et al., 2016). Along these lines, an observational study conducted among suicidal ED patients from Veterans Health Administration hospitals found that a brief structured intervention, including an outpatient appointment and telephone calls, increased engagement and reduced suicidal behaviors after discharge (Stanley et al., 2018). Building on the tradition of suicide prevention among high-risk individuals, our study contributes with data from the clinical practice suggesting that contact maintenance, by scheduling a single priority appointment before discharging suicide attempters from the ED, can lower the risk of suicide attempt relapse.

Suicide, a global public health concern, is the second cause of death among the Spanish youth (INE, 2017). In the United States, it is the only one, among the 10 leading causes of death, with an increasing rate over the last decade (Swanson, Bonnie, & Appelbaum, 2015). Suicide attempts are considered the most accurate markers for completed suicide: Attempters from a multicenter controlled study in England had a 43 times higher risk of suicide (Hawton et al., 2015). However, suicide attempts demand further attention beyond their predicting role. Not only they are an opportunity for prevention but also a frequent clinical entity by themselves (for example, around 10% of Spanish citizens have attempted suicide at least once) (Gabilondo et al., 2007), with an important associated burden of economic and emotional costs and a tendency to relapse. In fact, the presence of previous suicide attempts stood out as the major risk factor, with a HR of 2.32 in our adjusted models. In our study, more than 1 out of 5 attempts subsequently relapsed, and most reattempts took place during the first months of follow-up. This figure is consistent with that of a prospective study conducted in 150 Spanish subjects after hospital discharge (Tejedor, Díaz, Castillón, & Pericay, 1999), while a Danish cohort including 3,690 attempts exhibited an even higher risk, around 28% (Christiansen & Jensen, 2007).

As an addition, our study offers updated information on several clinical and sociodemographical risk factors for suicide and suicide attempts. As previously published in studies from a variety of international locations, female gender, previously diagnosed psychiatric disorders, and drug or alcohol abuse carried higher risk (Beghi, Rosenbaum, Cerri, & Cornaggia, 2013; Christiansen & Jensen, 2007; Holmstrand et al., 2015). A recent cohort study, conducted in Barcelona, Spain, found an increased risk in younger groups (Parra-Urbe et al., 2017), a finding that was absent in our study. However, differences could be explained because we considered age in years a continuous variable,

whereas the aforementioned study used age groups, established >60-year-old as the reference group and found an almost constant risk increase across the rest of age groups.

Our main strength is an easy-to-implement, well-defined intervention—an outpatient appointment with a psychiatrist within 7 days after the ED discharge. In the studied catchment area, ordinary consultations with specialists usually have waiting times over 19 days (Madrid's Health Results Observatory, 2017). We have found that median time to the first consultation after a hospital discharge, after a suicide attempt, decreased to 7 days after ARSUC program was implemented, over 50% of the subjects were seen in the desired time window, and compliance with the program is above 88% (E. Jiménez, G. Martínez-Alés, E. Román, M. P. Sánchez, B. De Dios C, Rodríguez-Vega et al., Under Review). Previous authors have emphasized the necessity to focus on suicide prevention at the ED, where most of the highest risk patients seek help, including those with a low adherence to conventional outpatient treatment (Larkin & Beautrais, 2010). In order to evaluate the program from a pragmatic point of view, we did not exclude any of the 2,347 suicide attempts treated during the study period, regardless of clinical profiles or inpatient admissions. As a consequence, our real-world results, obtained from a naturalistic setting, may provide critical evidence for decision makers. The effect estimates remained almost unchanged across the different univariate and multivariate models, suggesting an elevated robustness. The studied location, a catchment area with universal health coverage, combines different city districts and rural areas, including a wide range of ages, nationalities, and socioeconomical contexts (Hortas & Onrubia, 2017). In addition to the mentioned coincidence with previous results from other places and health systems, the heterogeneity of patient profiles and social contexts included provides grounds for our results to be considered widely generalizable, especially to settings with universal medical coverage.

Our study includes several limitations. First, we lack information regarding completed suicide among the study participants. As we have mentioned, suicide attempt and death by suicide are closely associated (Olfson, Wall, et al., 2017). Suicide is a less frequent phenomenon, and using reattempt as the main outcome allowed us to detect differences between groups. Nevertheless, certain authors have found differences between the profiles of suicide attempters and achievers (Parra-Uribe et al., 2013). Hence, further research should be conducted to ascertain to which level this program also reduces suicide risk. Secondly, it is possible that certain subjects relapsed and were evaluated at a different hospital during follow-up. However, we consider this possibility unlikely: As previously published, in our setting, treated suicide attempts are systematically referred to the catchment area's general hospital ED (Parra-Uribe et al., 2017). In addition, Madrid has high residential stability: For example, during 2017, only 2.88% of the studied area's population moved to a different catchment area (Ayuntamiento de Madrid). Besides, even though our reduced sensitivity to deaths and relapses evaluated elsewhere could lead to an underestimation of the incidence of relapse, this limitation would equally affect both treatment phases and thus not imply systematic error at the comparison level. Finally, the observational nature of our study makes it vulnerable to unascertained sources of bias. In particular, because we used a historical control group, we cannot rule out a potential sentinel or historical artifact. Notwithstanding, we consider this possibility unlikely because there is no evidence of a contemporary decrease in suicidal behaviors either in Madrid or elsewhere in Spain. On the contrary, data from outpatient and inpatient facilities suggest a general increase in such behaviors, in line with what has been observed in several samples from the United States (Olfson, Blanco, et al., 2017; Wester, Trepal, & King, 2017). A study conducted in Andalusia, Spain,

analyzed data on suicide attempts using telephone call records from the public emergency health care system: They found that the number and rate of attempts increased annually between 2010 and 2013, the last year of study (Mejías-Martín et al., 2017). Furthermore, data from nationwide electronic registries indicate that the number of hospital discharges including any form of suicide attempt as a diagnosis also increased annually, both in Madrid (1,747 registries in 2010 and 2,418 in 2015) and in Spain (11,476 registries in 2010 and 15,857 in 2015) (Ministerio de Sanidad, Consumo y Bienestar Social, 2018).

Further studies should include evaluations considering a longer follow-up, as previous research has called into question the long-term effectiveness of brief contact programs (Cebriá et al., 2015). Head-to-head comparisons with more complex interventions implemented in other catchment areas of the same location will help clarify the differential suicide risk reduction potential of their respective components (López-Castroman, Blasco-Fontecilla, Courtet, Baca-García, & Oquendo, 2015). Implementation studies in different locations, especially from LMIC, will define our findings' implications for Global Mental Health. As López-Castroman, Méndez-Bustos, et al., 2015 have pointed out, most of completed suicides take place in LMIC, while most suicide prevention research is conducted elsewhere. In addition, comparison studies across countries can yield findings concerning supra-individual determinants of interest (Susser & Martínez-Alés, 2018). For example, recent ecological studies suggest that the late 2000s financial recession had an increased impact on suicides in Spain (Fernández-Navarro et al., 2016) and that the substantial variation in national suicide rates can be partially explained by ecological variables (Schomerus et al., 2015). Suicide is, by definition, a "complex problem" that requires a careful assessment of the interactions between risk factors and multi-level preventive interventions (Hawton & Pirkis, 2017; Hegerl & Kohl, 2016).

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A Real-World Effectiveness Study Comparing a Priority Appointment, an Enhanced Contact Intervention, and a Psychotherapeutic Program Following Attempted Suicide

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ABSTRACT

Objective: To determine the comparative effectiveness of 3 real-practice preventive programs aimed at lowering the relapse risk following a suicide attempt: a single priority appointment with an outpatient psychiatrist, an enhanced contact intervention, and an individual psychotherapy program.

Methods: This observational study was conducted in a sample of 1,492 suicide attempters from 3 catchment areas in Madrid, Spain, between 2013 and 2017. Relapse was defined as an emergency department return after a new attempt within a 1-year follow-up. Kaplan-Meier survival functions were obtained by intervention, and Cox proportional hazard regression models were used to estimate unadjusted and adjusted risks of relapse by intervention. Sex- and age-stratified analyses were also conducted. Covariates were age, sex, history of suicide attempts, history of psychiatric disorders, main *ICD-10* psychiatric diagnostic groups, medical comorbidities, and family support.

Results: A total of 133 subjects (8.9%) relapsed. The psychotherapy group had a lower presence of known risk factors for suicide attempt. Individual psychotherapy and enhanced contact were more effective than a single priority appointment at reducing suicide reattempt, with a 40% lower relapse risk in adjusted models. Results did not differ after sex and age stratification.

Conclusions: In a naturalistic clinical setting, patients exposed to individual psychotherapy or an enhanced contact intervention had a similar, lower relapse risk than the single priority appointment group.

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Suicide, a global public health concern,¹ is the second leading cause of death among youth worldwide.² Attempted suicide, a much more frequent phenomenon with a rising incidence,³ is considered the most faithful risk marker of future suicide, with an associated 25-fold risk increase compared to the general population.⁴ Furthermore, self-inflicted harm itself entails relevant clinical and economic costs⁵ and represents 1.5% of all loss of disability-adjusted life-years according to Global Burden of Disease 2000.⁶ An attempted suicide entails a 5-year follow-up risk of relapse up to 35%, with most reattempts taking place during the first month after discharge.^{7,8}

Prevention of suicidal behaviors can be exercised at several levels of intervention.⁹ A number of population-level strategies, such as structurally limiting the access to suicide-by-jumping hotspots¹⁰ or legally restricting the size of acetaminophen packs,¹¹ can reduce the incidence of suicide attempts. At the individual level, enhancing contact between high-risk subjects and mental health providers can reduce attempted and completed suicide.¹²⁻¹⁴ As noted, discharge after an attempted suicide offers a critical opportunity for indicated tertiary prevention. Accordingly, postdischarge contact maintenance programs lower relapse risk.¹⁵⁻¹⁹ Manualized psychotherapies, including problem-solving,²⁰ cognitive-behavioral,²¹ dialectical behavior,^{22,23} or psychodynamic therapy,²⁴ are also seemingly effective. However, psychotherapy for suicidal behaviors has been called into question when compared to more feasible programs aimed at simply favoring continuation of care after discharge.²⁵ In a recent meta-analysis of randomized controlled trials (RCTs), the World Health Organization (WHO) Brief Intervention and Contact (BIC), a program of 9 follow-up contacts, significantly lowered the odds of suicide after an attempt by 80%, whereas cognitive-behavioral therapy (CBT) was not significantly protective.²⁶ Thus, although contact-enhancing and psychotherapeutic approaches seem promising, the adequate components and recommended length of interventions for recurring suicide attempt risk remain unclear. Most evidence concerning suicide prevention strategies comes from either non-experimental epidemiologic designs or RCTs. In clinical research, however, there is a growing call for comparative effectiveness studies including data from the real clinical practice.²⁷

Clinical Points

- Brief contact maintenance lowers the risk of relapse after a suicide attempt, but whether longer interventions, including telephone calls or psychotherapy, yield additional protective effects has heretofore been unclear.
- After a suicide attempt, prolonging contact maintenance and enhancing it with telephone calls or psychotherapy can lower the risk of a reattempt after hospital discharge.

This study compares 3 different interventions for suicide reattempt prevention in real-world settings. Compared programs following a suicide attempt include a single priority medical appointment within 7 days after discharge, a series of repeated in-person and telephone follow-up contacts, and an individual problem-solving psychotherapy intervention.

METHODS

Study Settings

In Spain, a National Health Service (NHS) funded by taxes provides universal access to medical care. The Community of Madrid's Health Council coordinates 25 health care catchment areas. Each area features a general hospital and includes a psychiatry department offering a range of inpatient and outpatient care resources to which general practitioners and other specialists refer patients with psychiatric needs.

Although enhancing the general population's access to proper longitudinal, articulated psychiatric care decreases suicidal behaviors, directly addressing suicide offers an additional protective effect.²⁸ Madrid's Mental Health Strategy 2010–2014 deployed the Suicide Risk Attention Program (ARSUIC, by its Spanish acronym) as an addition to its community-based mental health care service. This program prioritizes psychiatric attention to suicide attempters. Every hospital in Madrid adopted this program in 2012. Its basic measure, a scheduled meeting with an outpatient psychiatrist within the first 7 days after every suicide attempt, lowered the risk of reattempt by 25%.²⁹ Some hospitals have added complementary features to their particular suicide prevention programs. In general terms, the additional measures seek to either foster further contact maintenance with mental health practitioners via programmed telephone calls during the follow-up or provide patients with specific individual or group psychotherapy. In this study, we examine 3 different prevention strategies corresponding to 3 general hospitals covering 3 catchment areas located in the south, north, and west of Madrid, respectively.

Study Design and Subjects

We conducted an observational study. We included all suicide attempters who, after discharge, had entered each center's suicide prevention program between January 1, 2013, and December 31, 2016, and followed them for 1 year. We considered a suicide attempt any self-injurious act committed with at least some intent to die as a result of the act. Thus, we excluded individuals with suicidal ideation but

without suicidal behavior. The study protocol complies with the Declaration of Helsinki for Human Rights. Approval was obtained from the corresponding ethics committees in each catchment area. Data from patient records were anonymized before extraction of sociodemographic and clinical details.

Interventions

Participants from the northern catchment area received the strict ARSUIC intervention, a scheduled appointment with an ordinary psychiatrist at the corresponding Community Mental Healthcare Center (CMHC) within the first 7 days after hospital discharge. Thereafter, this intervention did not include further add-ons, nor did it have exclusion or inclusion criteria for participants, other than having been treated at the General Hospital due to an attempted suicide. As this program is widely implemented in Madrid, we considered it treatment as usual (TAU).

Participants from the southern catchment area received a modified ARSUIC intervention, adding individual psychotherapy. Inclusion criteria were to have attempted suicide, to be aged 18 years or older and not to have a concurrent ongoing therapeutic treatment at an outpatient clinic. The psychotherapy was administered at the general hospital. It included 2 months of weekly 30-minute individual, non-suicide-specific therapy sessions focused on problem-solving, stress reduction, and cognitive reformulation. Therapy sessions were conducted by trained clinical psychologists, under a general psychiatrist's supervision. Then, the patient was referred to a general practitioner or a CMHC. In case the participant failed to attend the sessions, reminder telephone calls were made from the hospital.

Participants from the western catchment area received an enhanced contact maintenance intervention framed within the greater "Código 100" (Code 100) Suicide Prevention Program, a strategy delivered in collaboration with Madrid's out-of-hospital emergency service to guarantee an appropriate continuity of care.³⁰ Inclusion criteria to Código 100 were to have attempted suicide, to be 18 years of age or older, and to sign an informed consent form. The intervention started with an appointment 3 days after discharge, followed by 6–12 months of an intensified frequency of outpatient visits depending upon the patient's severity and his or her personal preference, with a specifically devoted psychiatrist trained in suicide prevention. In addition, every patient received telephone calls from the hospital at follow-up months 1, 6, and 12. The content of these calls was explanatory and supportive, seeking to reassure patients, clarify their doubts regarding treatment, enhance their adherence to follow-up visits, and remind them of the available emergency treatment options in case of a new crisis. The intervention did not include a specific psychotherapeutic approach. Then, the patient continued usual treatment at a CMHC.

Measures

Our primary outcome was relapse after a suicide attempt, which we defined as being treated again at the reference hospital due to another suicide attempt after hospital

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Table 1. Baseline Clinical and Sociodemographic Covariates of the 1,492 Study Subjects, Overall and by Intervention

Variable	Overall	TAU	Psychotherapy	Enhanced Contact	χ^2/F	P^a
Total suicide attempters, n	1,492	788 (52.8% of overall)	523 (35.1% of overall)	181 (12.1% of overall)		
Age, mean (SD), y	40.9 (17.1)	41.0 (18.0)	40.3 (16.6)	42.6 (14.5)	1.25	.29
Female	1,040 (69.7)	540 (68.5)	360 (68.8)	140 (77.4)	5.77	.06
Personal history of a psychiatric disorder	976 (65.4)	554 (70.3)	255 (48.8)	166 (91.7)	0.00	.000
Main diagnosis at discharge						
No diagnosis	190 (12.7)	110 (14.0)	74 (14.2)	6 (3.3)	404.41	.000
Organic, including symptomatic, mental disorders ^b	11 (0.7)	6 (0.8)	5 (0.9)	0 (0.0)		
Mental and behavioral disorders due to psychoactive substance use ^c	172 (11.5)	94 (11.9)	68 (13.0)	10 (5.5)		
Schizophrenia, schizotypal, and delusional disorders ^d	28 (1.9)	15 (1.9)	12 (2.3)	1 (0.6)		
Mood (affective) disorders ^e	406 (27.2)	304 (38.6)	66 (12.6)	36 (19.9)		
Neurotic, stress-related, and somatoform disorders ^f	429 (28.8)	150 (19.0)	208 (39.8)	71 (39.2)		
Behavioral syndromes associated with physiologic disturbances and physical factors ^g	37 (2.5)	14 (1.8)	22 (4.2)	1 (0.6)		
Disorders of adult personality and behavior ^h	219 (14.7)	95 (12.1)	68 (13.0)	56 (30.9)		
Personal history of suicide attempts	583 (39.1)	272 (34.5)	145 (27.7)	85 (47.0)	246.21	.00
Concurrent alcohol or drug abuse	446 (29.9)	281 (35.7)	80 (15.3)	85 (47.0)	91.19	.00
Cohabiting	1,250 (83.7)	639 (81.1)	458 (87.4)	153 (84.5)	9.30	.01
Immigrant	483 (32.4)	132 (16.8)	200 (38.2)	151 (83.4)	322.47	.00
Comorbid medical conditions	551 (36.9)	481 (61.0)	39 (7.4)	31 (17.1)	422.87	.00

^a P values are obtained from Pearson χ^2 test or Fisher exact test for qualitative covariates and Wilcoxon signed-rank test for quantitative covariates.

^b*ICD-10* F00–F09. ^c*ICD-10* F10–F19. ^d*ICD-10* F20–F29. ^e*ICD-10* F30–F39. ^f*ICD-10* F40–F48. ^g*ICD-10* F50–F59. ^h*ICD-10* F60–F69.

Abbreviation: TAU = treatment as usual.

discharge and during a 1-year follow-up. Time to relapse was obtained from the hospital's records. For subjects experiencing multiple relapses, we retained only the first one after entrance into the study.

Data on clinical and sociodemographic variables of prognostic interest were obtained from pre-discharge semistructured interviews, regularly performed by psychiatrists and stored in computer databases for clinical purposes. We selected the following sociodemographic variables: age (continuous variable), sex, immigrant status, and cohabitation status (binary variables). Clinical variables recorded as dichotomous included personal history of a diagnosed psychiatric disorder, personal history of suicide attempts, concurrent alcohol or drug consumption at the moment of the attempt, presence of comorbid medical conditions, and main diagnosis at discharge, encoded according to *ICD-10*, chapter V, F10–F69 diagnostic groups (mental and behavioral disorders due to psychoactive substance use; schizophrenia, schizotypal and delusional disorders; mood disorders; neurotic, stress-related, and somatoform disorders; behavioral syndromes associated with physiologic disturbances and physical factors; and disorders of adult personality and behavior).³¹

Data Analyses

Continuous variables were reported as mean (standard deviation) and categorical variables as proportions. To analyze baseline differences in clinical and sociodemographic variables between the intervention groups, we used Wilcoxon signed-rank, Pearson χ^2 , and Fisher exact tests.

We then conducted a survival analysis. Subjects who had not relapsed within 1 year of follow-up were censored. We obtained Kaplan-Meier estimates of the survival function by treatment group. We tested the difference using log rank

tests. To control for potential confounders, we conducted Cox proportional hazards regressions and obtained crude and adjusted risk estimates (hazard ratios [HRs]) for the different groups. For the multivariate model, we retained those covariates remaining significant to the $P < .10$ level, utilizing a non-automatic method for their introduction, as well as those variables considered to be clinically relevant according to prior knowledge. We followed widely accepted schemes for the adjustments.³² Proportional hazards assumption fulfillment was ascertained both through graphic methods and using the Schoenfeld test. Finally, we obtained number needed to treat (NNT) estimates for both interventions compared to TAU using an accepted method for studies in which the outcome of interest is the time to an event.³³

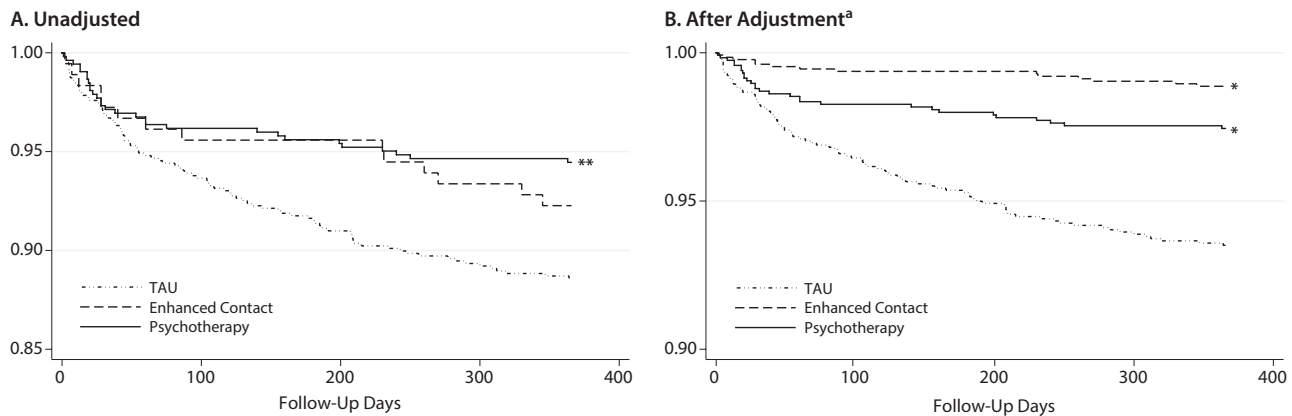
Sex and age-group differences exist in suicide and self-harm rates, and recent research shows that the young women stratum is becoming increasingly more affected.^{34,35} Accordingly, we conducted sex- and age group-stratified Cox proportional hazards regressions seeking for differences between programs across subgroups. We defined 3 different subgroups: female and ≤ 35 years old, female and > 35 years old, and male. To keep reasonable statistical power for comparisons, we did not differentiate age groups within males. Analyses were carried on Stata v13 software.³⁶

RESULTS

Clinical and Demographic Characteristics

We included data from 1,492 patients who had attempted suicide and subsequently entered the suicide prevention program at 1 of the 3 hospitals between January 1, 2013, and December 31, 2016. Table 1 summarizes baseline characteristics of the study subjects, both globally and per intervention group.

Figure 1. Kaplan-Meier Survival Function Estimates by Intervention



^aAdjusted by sex, concurrent alcohol or drug abuse, personal history of suicide attempts, presence of a mood disorder diagnosis, and presence of a personality disorder diagnosis

* $P < .05$ (log rank test) vs TAU.

** $P < .01$ (log rank test) vs TAU.

Abbreviation: TAU = treatment as usual.

Intervention Group Baseline Differences

Baseline covariates showed comparable intergroup age distribution and a higher percentage of females in the enhanced contact group, along with several differences regarding clinical and social covariables. Subjects receiving TAU (the majority of the study participants) had proportions of psychiatric history (70.3%), previous suicide attempts (34.5%), and concurrent alcohol or drug abuse (35.7%) that fall roughly halfway between that of the other two treatment groups, suggesting that this cohort had an intermediate level of clinical severity. As for social correlates, subjects receiving TAU had the lowest levels of both immigration and household cohabitation. The sample receiving psychotherapy, formed by one-third of the subjects, had the lowest prevalence of the aforementioned clinical covariables, intermediate levels of immigration, and relatively high levels of cohabitation. Participants receiving enhanced contact, the smallest group, had the highest prevalence of previous psychiatric conditions, immigration, and previous suicide attempts and drug or alcohol abuse. Regarding main diagnoses at discharge, the psychotherapy and enhanced contact groups had similar rates of neurotic, stress-related, and somatoform disorders, and the latter also showed a high presence of disorders of adult personality and behavior, while TAU participants were more frequently diagnosed as having mood disorders. These findings, suggesting the psychotherapy group included a less severely ill sample, make sense as this intervention included only subjects who did not have an ongoing outpatient therapeutic treatment.

Follow-Up and Relapse

A total of 133 subjects (8.9%) experienced a relapse during follow-up. TAU had twice the crude incidence of the psychotherapy group, while the enhanced contact group had an intermediate figure. Mean (95% CI) days of follow-up were TAU: 335.8 (329.7–341.9), enhanced contact: 347.4

(337.2–357.6), and psychotherapy: 349.6 (343.8–355.3) for global: 342.0 (338.0–346.1).

Curves obtained from Kaplan-Meier survival probability function estimates per intervention group and multivariate adjusted survivor functions are presented in Figure 1. Differences between TAU and both psychotherapy and enhanced contact groups in Kaplan-Meier estimates are statistically significant (log rank test $P = .001$).

Table 2 displays results arising from Cox proportional hazards models, including unadjusted and adjusted estimates. Univariate regressions showed an association between a higher risk of relapse and several measured risk factors: a personal history of suicide attempts, concurrent alcohol or drug abuse, and a comorbid condition. Among psychiatric conditions diagnosed, mood and personality disorders stood out as risk factors, and adjustment and stress disorders behaved as protective factors. Immigration also showed a protective effect. On the other hand, female sex did not achieve statistical significance and neither did cohabitation or age in years. We fitted a subsequent multivariate regression by following a non-automatic method and delivered an adjusted model. We controlled for age, sex, previous suicide attempts, alcohol or drug abuse, and mood (affective) and personality disorders. The fulfillment of the proportional hazards assumption was checked: Schoenfeld residuals test P values of .26 and .13 were found for the univariate and multivariate models, respectively. Using the adjusted regression, we estimated the NNT (95% CI) for each intervention compared to TAU, resulting in 6.7 (3.3–100.0) for psychotherapy and 5.3 (2.6–1,000.0) for enhanced contact. An alternative multivariate model including the more general personal history of a psychiatric disorder instead of specific diagnoses resulted in similar estimates and served as a sensitivity analysis (Supplementary Table 1).

We obtained age- and sex-stratified multivariate estimates (Table 3). Although the smaller resulting sample of subjects

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Table 2. Risk of Relapse During Follow-Up^a

Variable	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Relapsed during follow-up		
TAU: n=90 (11.4)	1	1
Psychotherapy: n=29 (5.5)	0.47 (0.31–0.72)**	0.62 (0.40–0.97)*
Enhanced contact: n=14 (7.7)	0.66 (0.38–1.16)	0.56 (0.32–1.00)*
Age	0.99 (0.98–1.00)	0.99 (0.98–1.00)
Female	1.27 (0.86–1.87)	1.32 (0.88–1.98)
Immigrant	0.68 (0.46–1.00)*	...
Cohabiting	1.10 (0.68–1.77)	...
Personal history of a psychiatric disorder	1.86 (1.24–2.80)**	...
Diagnosis at discharge		
No diagnosis	0.67 (0.37–1.21)	...
Mental and behavioral disorders due to psychoactive substance use ^b	1.38 (0.86–2.22)	...
Mood (affective) disorders ^c	1.70 (1.20–2.42)**	1.60 (1.10–2.32)**
Neurotic, stress-related, and somatoform disorders ^d	0.35 (0.21–0.58)**	...
Disorders of adult personality and behavior ^e	1.52 (1.00–2.32)*	1.82 (1.14–2.91)**
Personal history of suicide attempts	1.89 (1.34–2.65)**	1.63 (1.15–2.31)**
Concurrent alcohol or drug abuse	1.77 (1.35–2.67)**	1.64 (1.13–2.38)**
Comorbid medical condition	1.73 (1.23–2.43)**	...

^aHazard ratio (HR) values were derived from a Cox proportional hazards model that included time to relapse as the outcome and the clinical and sociodemographic covariates as predictors. Treatment as usual (TAU) is the reference. The multivariate model is age- and sex-adjusted and includes variables significant at the $P \leq .05$ level following a non-automatic adjustment method.

^bICD-10 F10–F19. ^cICD-10 F30–F39. ^dICD-10 F40–F48. ^eICD-10 F60–F69.

* $P \leq .05$. ** $P \leq .01$.

Table 3. Risk of Relapse During the Follow-Up by Patient Sex and Age Groups^a

Variable	Male (n = 452, 30.3% of Overall)	Female ≤ 35 y (n = 452, 30.3% of Overall)	Female > 35 y (n = 588, 39.4% of Overall)
Intervention			
TAU	1	1	1
Psychotherapy	0.62 (0.37–1.04)	0.57 (0.27–1.20)	0.65 (0.32–1.34)
Enhanced contact	0.57 (0.31–1.08)	0.66 (0.22–1.96)	0.54 (0.25–1.19)
Mood (affective) disorders ^b	1.54 (0.96–2.32)	1.61 (0.75–3.43)	1.54 (0.83–2.85)
Disorders of adult personality and behavior ^c	2.09 (1.25–3.51)	1.91 (0.75–3.43)	2.29 (1.11–4.70)*
Personal history of suicide attempts	1.73 (1.16–2.59)**	1.48 (0.79–2.77)	1.93 (1.13–3.29)*
Concurrent alcohol or drug abuse	1.73 (0.98–2.32)	1.96 (0.45–2.02)	1.64 (1.14–3.35)*

^aValues are shown as hazard ratio (95% CI). The multivariate model is derived from an age- and sex-adjusted Cox proportional hazard multivariate model, with time to relapse as the outcome and treatment as usual (TAU) as the reference, and includes the same covariates as the multivariate model in Table 2.

^bICD-10 F30–F39.

^cICD-10 F60–F69.

* $P \leq .05$.

** $P \leq .01$.

per stratum made the confidence intervals wider, the effect estimates of both interventions were not altered across sex groups or between younger and older females. Mood (affective) and personality disorders, previous suicide attempts, and concurrent alcohol or drug abuse also had comparable effect sizes with wider confidence intervals across groups.

DISCUSSION

In this observational study, 2 programs—a 2-month weekly problem-solving psychotherapy intervention followed by scheduled telephone calls (psychotherapy) and an early appointment followed by a 6- to 12-month schedule of in-person visits and telephone calls (enhanced contact)—lowered the risk of relapse after an attempted suicide by 38%

and 44% during a 1-year follow-up, respectively, compared to a single priority outpatient psychiatry appointment within 7 days (TAU). The NNT estimates were 6.7 (psychotherapy) and 5.3 (enhanced contact). Building on the tradition of natural experiments including real-world clinical settings,²⁷ our study contributes to the identified need of head-to-head comparative effectiveness studies between detailed suicide prevention programs to develop a means for a better understanding of the underlying mechanisms of different interventions.³⁷

The period following discharge after a suicide attempt is a time of extremely high relapse risk.³⁸ In this cohort, 8.9% of the subjects relapsed during a 12-month follow-up, a somewhat lower figure than reported during longer follow-ups in comparable settings.³⁹ This difference is probably because contact maintenance with suicide attempters

can reduce repetition of suicidal behaviors.³⁷ Our control intervention, an early follow-up after self-harm, has shown effectiveness in reducing recurrence both in our setting²⁷ and in others.⁴⁰ Also, we did not include subsequent relapses, hence excluding attempts conducted by heavy repeaters.

In keeping with the literature,^{16,41,42} our results suggest that repeated scheduled telephone calls lower postdischarge relapse risk. Some psychotherapeutic approaches have proved useful in lowering suicide risk among certain subtypes of patients.^{21–23} However, in our study, the group receiving individual problem-solving psychotherapy did not significantly differ from those only receiving intensive contact maintenance. This finding is unsurprising: RCTs and systematic reviews have found no benefits in adding psychotherapy to conventional treatments for unselected suicidal subjects.^{25,43,44}

Our study has limitations we would be remiss not to report. To have enough power to detect differences between groups, we chose suicide reattempt as our outcome of interest and did not include information concerning death by suicide, an important but infrequent event. As we have mentioned, there is a close association between suicide attempt and death by suicide.^{4,45} For example, Finkelstein et al⁴⁶ reported that first-time self-poisoning survivors had a completed suicide HR of 41.96 when compared to controls. Nonetheless, differences between suicide attempters and completers have been reported elsewhere.^{38,47} Thus, we can focus only on the programs' protective role against attempted suicide. As this was a real-world study, we did not randomly assign the interventions. Instead, each center had different criteria for inclusion. As a matter of fact, baseline characteristics showed differences across groups. Accordingly, we fitted 2 different multivariate models and obtained similar estimates across models, suggesting robust results. Nevertheless, we cannot rule out residual confounding or selection bias due to unmeasured correlates such as lethality, suicide attempt method, or family history of suicide, and therefore the effect estimates should be carefully considered. A comparison with historical controls from each catchment area might provide useful additional effect estimates. Also, there is a possibility that certain relapses were evaluated at a different hospital during follow-up. In our context, this possibility is unlikely. First, as other authors from comparable areas of the same health care system have previously published, treated suicide attempters are systematically referred to the subject's catchment area's general hospital.⁸ Second, Madrid's population shows high residential stability through time: per official data from 2017,⁴⁸ only 3.49% of the people living in 1 of the 3 studied catchment areas moved to a different district. All in all, this possibility does not differentially affect our studied catchment areas; thus, we consider our comparative effectiveness estimates internally valid. Lastly, it has been suggested that, just as in most complex phenomena, risk factors for suicide and suicidal behaviors act not only at the individual level but also at overarching ecological levels.^{9,45,49,50} For example, the frequency of suicide ideation and attempts shows remarkable differences

across countries.⁵⁰ However, the 3 intervention groups are contemporary and belong to comparable catchment areas of the same city, so we consider differences in such factors unlikely.

The strictly naturalistic enrollment of the study yields results that can be considered directly applicable. Most clinical guidelines prioritize evidence arising from RCTs. However, although strict inclusion criteria, randomization, and close follow-up provide highly internally valid efficacy estimates, their ability to also produce clinically generalizable effectiveness estimates has been called into question.²⁷ In line with this similarity, effectiveness estimates from clinical settings are progressively becoming a valuable source, sought after by decision makers.⁵¹ This real-world approach most likely captures an intervention's actual impact in the management of most psychiatric conditions, deeply shaped by interactions with the environment (such as suicide risk or schizophrenia).⁵² As previously mentioned, the results are in line with most published research on suicide attempters regarding both the sample's characteristics (a mean age of around 40 years, a higher percentage of females, frequent co-occurrence of alcohol or drug consumption, and main diagnoses of mood, adjustment, and personality disorders^{8,12,53}) and the effect estimates of the implemented measures. Hence, we consider these estimates as widely generalizable, especially to contexts where, as in ours, a catchment area-based public system provides universal coverage to the population. Besides, patients were enrolled right before discharge from the general hospital, mostly at the emergency department. Our study therefore supports recent studies' recommendation of a focus toward suicide prevention at such settings because of the concentration of subjects with high suicide risk and low adherence to outpatient resources.⁵⁴

Suicide behaviors are a growing, critical public health issue: in the United States, 1.1 million persons attempt suicide every year.⁵⁵ Even though several preventive strategies have proved useful at lowering such behaviors, selecting and promoting measures that entail an additional staff burden require both political will and adequate evidence. Because RCTs of interventions designed to prevent suicide attempts often have ethical limitations,⁵⁶ pragmatic designs using real-world data offer an advantageous approach. Nonetheless, the question of if psychotherapy adds value to contact maintenance for suicidal behavior prevention remains partially unanswered.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.

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Supplementary Material

Article Title: A Real-World Effectiveness Study Comparing a Priority Appointment, an Enhanced Contact Intervention, and a Psychotherapeutic Program Following Attempted Suicide

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List of Supplementary Material for the article

1. [Table 1](#) Risk of relapse during the follow-up, derived from a Cox proportional hazard model including time to relapse as the outcome and the clinical and sociodemographic covariates as predictors.

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Supplementary Table 1: Risk of relapse during the follow-up, derived from a Cox proportional hazard model including time to relapse as the outcome and the clinical and sociodemographic covariates as predictors. Treatment as usual (TAU) is the reference. This alternative multivariate model is age and gender-adjusted and includes personal history of a psychiatric disorder, instead of specific diagnostic groups. (* $p \leq 0.05$; ** $p \leq 0.01$)

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
TAU	1	1
Psychotherapy	0.47 (0.31-0.72) **	0.56 (0.37-0.87)**
Enhanced Contact	0.66 (0.38-1.16)	0.56 (0.31-0.98)*
Age in years	0.99 (0.98-1.00)	0.99 (0.98-1.00)
Female	1.27 (0.86-1.87)	1.35 (0.90-2.01)
Immigrant	0.68 (0.46-1.00) *	-
Cohabitation	1.10 (0.68-1.77)	-
Personal history of a psychiatric disorder	1.86 (1.24-2.80) **	1.42 (0.92-2.19)
Personal history of suicide attempts	1.89 (1.34-2.65) **	1.56 (1.09-2.23)**
Concurrent alcohol/ drug abuse	1.77 (1.35-2.67) **	1.54 (1.06-2.22)*
Comorbid medical condition	1.73 (1.23-2.43) **	-

Putting Psychosis Into Sociocultural Context

An International Study in 17 Locations

Ezra Susser, MD, DrPH; Gonzalo Martínez-Alés, MD, MSc

It seems eminently plausible that there should be variation in the incidence of psychoses across the globe. Nonetheless, we know little about the nature and scope of such variation, and what we do know is often misunderstood. The landmark World Health Organization Ten Country Study,¹ published in 1992, pioneered a strategy for comparing the incidence of treated cases of psychoses across multiple settings in different countries. It obtained incidence rates for schizophrenic disorders from 8 diverse settings, including rural and urban Chandigarh, India; Nagasaki, Japan; European locations; and North American settings. The authors described the rates of schizophrenic disorders as “surprisingly similar”^{1(p90)} and further remarked that this finding would “not easily lend itself to an interpretation.”^{1(p91)} They did not claim that schizophrenia has the same incidence across the globe, a common misunderstanding of the study. (Indeed, Chandigarh was the only site in a low-income country that yielded any incidence rates¹; in later analyses, a distinctive psychotic disorder subtype was found to be more common there.²) A subsequent comprehensive review³ of a large number of studies concluded that the incidence of schizophrenia shows substantial variation by place. A specific example was higher incidence rates in more urban locales. However, to our knowledge, there has not been another attempt to date to demonstrate variation in psychosis incidence within a single study of multiple locations in several countries using comparable methods in each place.



Related article page 36

In this issue of *JAMA Psychiatry*, Jongsma et al⁴ publish an extraordinary study designed to compare incidence rates of all psychotic disorders in 17 settings in 6 countries. The study included 2774 people with psychotic disorders detected at the time that the patients presented for treatment at mental health services. This study differs in important ways from the Ten Country Study.¹ The settings are less diverse, with all but 1 located in western Europe and more than half located in either Spain (n = 6) or Italy (n = 3). This reduces sociocultural contrasts but made the study more tractable for examining measured dimensions of social context that might explain variation across settings. Recent developments in theory and empirical research facilitated the choice of contextual measures.⁵ Moreover, the study is an integral part of a broader scientific initiative focused on gene-environment interactions, the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions. The study also reports on individual characteristics (age, sex, and racial/

ethnic minority status), but the comparisons across settings in different countries were the most novel contribution.

The initial results are intriguing and somewhat surprising. Jongsma et al⁴ report a striking 10-fold variation across study settings, from 6.3 to 61.4 cases per 100 000 person-years in the crude incidence of all psychotic disorders for people aged 18 to 64 years. This was reduced to approximately 8-fold variation after accounting for age, sex, and (at least crudely) racial/ethnic minority status. Results were not entirely consistent at the setting level across 3 interrelated measures of social context. A strong and important result was that some of the variation was explained by the association of a higher proportion of owner-occupied homes, a proxy for social stability and cohesion, with lower incidence of psychosis. In unadjusted analyses, a higher proportion of single-person households, a proxy for social fragmentation, was associated with higher psychosis incidence, but this characteristic did not have a detectable effect on incidence after adjustment for home ownership. Additional unadjusted analyses showed that higher unemployment, a proxy for social deprivation, was unexpectedly associated with lower incidence of psychotic disorders, but this also had no detectable effect after adjustment for home ownership. Another unexpected result was that higher population density was not associated with higher psychosis incidence in Spain, Italy, or all settings combined; however, population density was associated with psychotic disorder incidence in England and the Netherlands, which is consistent with previous studies.³

These results⁴ should generate vigorous debate and further analysis as we seek to explain them. One possibility might be that the sociocultural contexts of Spain and Italy are distinctive in ways that were not captured by measurements at the level of individual settings or catchment areas. A related point is that the relationships between the measures chosen might vary across levels of analysis. For example, Spain has relatively high levels of home ownership and unemployment, and these 2 variables are generally correlated with one another at the country level in western Europe.⁶ This might partly explain why unemployment was related to lower incidence across settings from various countries before adjustment for home ownership. There might also be interactions between individual-level and setting-level characteristics that could not be captured in the analysis; for example, living in a single-person household might have a different meaning when it is more or less common within a setting.⁵ Finally, setting-level measures might not capture the substantial heteroge-

neity of local contexts within a study setting, nor the relation of individuals to those contexts.⁷

We would be remiss if we did not comment on some of the potential sources of artifactual variation, which will surely be hotly debated. Most are addressed by the authors, but we wish to emphasize 3 that might require further attention. One concern is that the generally low incidence rates in Italy and Spain (range, 6.3-21.5 cases per 100 000 person-years) are underestimated. Previous, partially overlapping studies from Italy have reported similar findings.⁸ However, in Spain questions might be raised about the outlier finding of very low incidence in Santiago (6.1 cases per 100,000 person-years). Also, in the metropolitan area of Madrid, patients are not necessarily restricted to the use of mental health services within a specific catchment area.⁹ In addition, the remarkably low median duration of untreated psychosis in Madrid (2.5 weeks) is puzzling, as it is lower than all other sites, which had a median duration of untreated psychosis of 8 weeks. A second concern is that key setting-level variables were derived from data at the provincial level, a broader region than the catchment area. A third concern is that the authors⁴ modified the approach of the World Health Organization Ten Country Study, which had aimed to identify the first treatment contact that patients had made in any kind of health care service; Jongsma et al⁴ instead covered only contacts with mental health services. It can be challenging to identify all incident treated psychoses, even with a broader approach to data collection.¹⁰ It is therefore possible that this study underestimates incidence to variable extents in different settings.

Despite these and other concerns, it seems likely that much of the unexplained variation reported here is real. It also seems

likely that part of it is explained by as-yet unidentified socio-cultural differences between settings.

There is a long history of research on the social determinants of psychoses. Building primarily on the tradition of social ecologic research,¹¹ this study shows how far this field has advanced and how far it has yet to go. We now have strong evidence that social experiences influence individual brain development¹² and some evidence about the kinds of social context that may play a role in the trajectory toward psychosis onset.⁵ Our understanding of how the effect of individual experiences interact with or reflect the broader social context at multiple levels is ever advancing but quite incomplete.⁷ These results of the study by Jongsma et al⁴ underscore the need to continue to refine both theories and measurements of the relationships between sociocultural environmental factors and psychoses,⁵ to seize opportunities to examine interactions at multiple, strategically chosen levels via strong study designs, and to use new opportunities to extend these studies across the globe. That is no small task, but it is not inherently more difficult than making advances in other crucial areas, such as neurodevelopmental neuroscience. Finally, these results reinforce the importance of integrating developmental neuroscience and genomics with sociocultural research; the location of this study within a broader initiative, the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions, represents a step toward that goal.

Like the World Health Organization Ten Country Study,¹ this study⁴ raises more questions than it answers, demonstrating how much we can still learn. We hope that it will spur further international efforts to explore how variation in sociocultural environments might be associated with psychosis incidence.

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Suicide: Contexts and persons[☆]



Suicidio: contextos y personas

Dear Editor,

Suicide is a public health problem of the highest magnitude. Of the 10 most common causes of death worldwide, suicide alone is the only one which has not decreased during the last decade, despite the enormous scientific accomplishments relating to it.¹ Despite the huge investment in research projects and increasing implementation of specific programmes, the prevention of suicide is a yet ‘‘unresolved clinical requirement’’.² In their editorial, Barrigón and Baca-García proposed that some of the bases upon which the field of investigation into the prevention of suicide has been constructed over the last few decades should be reformulated.³ They suggested that the general framework of clinical research be based on individuals, and recommended evolving from the isolated study of risk factors to the definition of their algorithms, based on data processing with automatic learning techniques and personalised monitoring supported by new technologies.

We believe that the study and prevention of suicide should necessarily include a populational standpoint to understand and reduce their risk factors on an individual level. Since the publication of the Durheim sociological studies it has been accepted that suicide is a phenomenon where the rate at least partially responds to certain supraindividuals.⁴ Some examples support this idea: several countries, such as Lithuania have standardised rates of suicide 5 times higher than other countries, like for example, Greece.⁵ In U.S.A. the suicide rates in rural areas are double those of urban areas.⁶ Indeed, within the same city, London,

areas with higher ecological rates of social deprivation are associated with higher suicide rates.⁷

Modern epidemiology attempts to define what elements have a causal relationship with the presentation of diseases in populations. Development has led to paradigms which have determined the research questions and consequently the response obtained.⁸ The initial idea was eminently ecological: it is believed that modern epidemiology emerged with John Snow and spatial distribution of epidemics of cholera in 19th century London. After this, the discovery of the tubercle bacillus and other infectious agents paved the way for the molecular era. Lastly, as a result of the second world war, epidemiology of chronic non-transmissible diseases appeared. These are centred upon the subject, their behaviour and individual risk factors such as a tobacco habit or high blood pressure. Characteristically, each era of epidemiology has focused on a single level of study (ecological, molecular, individual), negating all others to a greater or lesser degree.⁸ Epidemiology of risk factors has therefore produced a sizable body of eminently individual causal knowledge. At present, however, we are witnessing the growth of an integral approach to epidemiology which some people have called multilevel epidemiology, and which proposes that disease phenomena respond to causal patterns with rationale that act at different molecular, individual and populational levels which interact on complex hierarchical networks.⁹ From this outlook, information collected by ecological variables, far from being considered an exchangeable estimator with data collected on an individual level, enjoy their own relevance for proper understanding of the sociological motives of the disease.¹⁰

One initiative stands out as an optimisation opportunity when giving ecological causal factors the place they have earned: overall mental health collaborations. By definition, an epidemiological study is able to analyse potentially causal relationships when a control exists with which to generate comparison. Through the inclusion of different research contexts using ecological measurements to pinpoint the differences between contexts, we may calculate the role played by supraindividual variables on suicide rates.

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The study of all disease phenomena may benefit from a multilevel approach. In a recent example, the EU-FEI international consortium published enormous differences in the rate of psychosis between different European regions.¹¹ Their results also suggested that one of the best established risk factors for psychosis, the urban environment, probably does not have the same impact in Northern compared with Southern Europe.

Populational and individual outlooks will need to be included to understand the enormous variability in suicide rates and to improve our ability to prevent it. Ecological variables provide irreplaceable information for decision-making by clinicians, managers and politicians.

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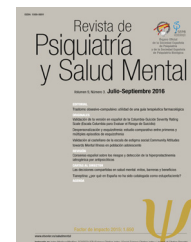
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CARTA AL DIRECTOR

Suicidio: contextos y personas

Suicide: Contexts and persons

Sr. Director:

El suicidio es un problema de salud pública de primera magnitud. Destaca por ser la única, entre las 10 causas de muerte más frecuentes a nivel mundial, cuya incidencia no ha descendido en la última década, pese a la enorme producción científica relacionada¹. Se considera que, pese a la gran inversión en proyectos de investigación y la creciente implementación de programas específicos, la prevención del suicidio es una «necesidad clínica no resuelta»². En su artículo editorial, Barrigón y Baca-García proponen reformular algunas de las bases sobre las que se ha construido el campo de investigación sobre la prevención de suicidio a lo largo de las últimas décadas³. Sugiriendo como marco general la investigación clínica basada en individuos, recomiendan evolucionar desde el estudio aislado de factores de riesgo a la definición de algoritmos de los mismos, basados en el tratamiento de datos con técnicas de aprendizaje automático y en el seguimiento personalizado apoyado en nuevas tecnologías.

Consideramos que es necesario incluir, en el estudio y prevención del suicidio, una perspectiva poblacional para comprender y reducir sus factores de riesgo a nivel individual. Desde la publicación de los estudios sociológicos de Durkheim se acepta que el suicidio es un fenómeno cuya incidencia responde, al menos parcialmente, a determinantes supraindividuales⁴. Ciertos ejemplos apoyan este planteamiento: algunos países, como Lituania, tienen incidencias estandarizadas de suicidio 5 veces superiores a la de otros, como Grecia⁵. En EE.UU., las tasas de suicidio en áreas rurales duplican las urbanas⁶. Incluso dentro de una misma ciudad, Londres, las zonas con mayores índices ecológicos de privación social asocian las mayores tasas de suicidio⁷.

La epidemiología moderna trata de definir qué elementos tienen una relación causal con la aparición de las enfermedades en las poblaciones. En su desarrollo se han sucedido paradigmas que han determinado las preguntas de investigación y, con ello, las respuestas obtenidas⁸. El planteamiento inicial fue eminentemente ecológico: se considera que la epidemiología moderna nació con John Snow y la distribución espacial de las epidemias de cólera en el Londres del siglo XIX. Posteriormente, el descubrimiento del bacilo

tuberculoso y otros agentes infecciosos dio paso a la era molecular. Por último, a raíz de la segunda guerra mundial, apareció la epidemiología de las enfermedades crónicas o no transmisibles, centrada en el sujeto, su conducta y los factores de riesgo individuales, como el tabaquismo o la hipertensión arterial. Característicamente, cada era de la epidemiología se ha centrado en un solo nivel de estudio (ecológico, molecular, individual), negando los demás en mayor o menor medida⁸. Así, la epidemiología de los factores de riesgo ha producido un gran cuerpo de conocimiento causal eminentemente individual. En este momento, no obstante, atendemos al crecimiento de una concepción integradora de la epidemiología, que algunos han llamado epidemiología multinivel, y que considera que los fenómenos de enfermedad responden a esquemas causales con determinantes que actúan a diferentes niveles, molecular, individual y poblacional, interactuando en complejas redes jerárquicas⁹. En este planteamiento, la información recogida por variables ecológicas, lejos de ser considerada un estimador intercambiable con datos recogidos al nivel individual, goza de su propia relevancia para el correcto entendimiento de los determinantes sociológicos de la enfermedad¹⁰.

Una iniciativa destaca como oportunidad de mejora a la hora de colocar a los factores causales ecológicos en el espacio que les corresponde: las colaboraciones de salud mental global. Por definición, un estudio epidemiológico es capaz de analizar relaciones potencialmente causales cuando consta de un control con el que generar comparaciones. A través de la inclusión de diferentes contextos de investigación, utilizando medidas ecológicas que recojan las diferencias entre contextos, podremos estimar el papel que juegan las variables supraindividuales en la incidencia del suicidio. El estudio de todos los fenómenos de enfermedad se puede beneficiar de un planteamiento multinivel. En un ejemplo reciente, el consorcio internacional EU-GEI ha publicado enormes diferencias en la incidencia de psicosis entre diferentes regiones de Europa¹¹. Sus resultados, además, sugieren que uno de los factores de riesgo mejor establecidos para la psicosis, el ambiente urbano, probablemente no se comporte igual en el norte y el sur de Europa.

Será necesario incluir las perspectivas poblacional e individual para comprender la enorme variabilidad en las incidencias de suicidio y mejorar nuestra capacidad para prevenirlo. Las variables ecológicas proporcionan información irremplazable para la toma de decisiones por parte de clínicos, gestores y políticos.

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¿Individuos suicidas y poblaciones suicidas?

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Señor Director: El suicidio es un problema de Salud Pública de primera magnitud¹. En nuestro país, pese a la tradicional baja incidencia de suicidio en comparación con otros países europeos, supone la primera causa de muerte por causa externa². Además, al afectar especialmente a personas jóvenes, el suicidio asocia enormes pérdidas económicas (se estima que ocasiona el 1,5% de todos los años de vida ajustados por calidad perdidos a nivel mundial) y un gran impacto emocional a nivel sociofamiliar. A lo largo de las últimas décadas, la investigación en prevención del suicidio se ha centrado en identificar factores de riesgo individuales para prevenir el suicidio a nivel del sujeto³. Un ejemplo contemporáneo es el proyecto Army STARRS, considerado el mayor estudio de la historia de salud mental en personal militar, que estudia variables predictores del suicidio entre excombatientes del ejército de los Estados Unidos⁴. La incidencia de suicidio entre militares norteamericanos es muy elevada: provoca más muertes que el combate. Fruto del conocimiento acumulado, se han implementado programas de contacto y psicoterapia orientados a individuos de alto riesgo^{5,6}. Sin embargo, pese a los esfuerzos en investigación, la prevención del suicidio sigue considerándose una “necesidad clínica no resuelta”⁷. En Estados Unidos es la única, de entre las principales causas de muerte, cuya incidencia está en aumento⁸.

Una de las máximas en el estudio de la incidencia del suicidio es que se trata de un fenómeno sujeto, en cierta medida, a determinantes que intervienen a un nivel por encima del individual. La investigación de las causas sociológicas del suicidio comenzó

con la publicación del libro seminal *Le suicide*, de Émile Durkheim, el primero en relacionar las tasas de incidencia con fenómenos como guerras o depresiones económicas⁹. Esta perspectiva ha recuperado actualidad, recientemente, con el vivo debate acerca de la relación entre la recesión económica internacional y un posible aumento de casos¹⁰. El estudio de los determinantes poblacionales de los fenómenos de enfermedad, de forma separada de los determinantes individuales, tiene siglos de tradición. La epidemiología, la ciencia que estudia la distribución de las enfermedades y sus causas en la población, tuvo originalmente una vocación eminentemente ecológica contrapuesta, en muchos casos, a la visión individual de la medicina clínica. Tomando las palabras de Geoffrey Rose: “¿Por qué algunos individuos tienen hipertensión? es una pregunta diferente de ¿Por qué algunas poblaciones tienen mucha hipertensión? (...) requieren diferentes tipos de estudio y tienen diferentes respuestas”¹¹. Sin embargo, la epidemiología clínica de los últimos 50 años se ha centrado en identificar factores acumulativos de riesgo individual de las enfermedades, excluyendo las causas ecológicas de su marco conceptual¹². Este escotoma no es un fenómeno raro en investigación: de acuerdo con Mervyn y Ezra Susser, es característico que la mayor parte de producción científica se desarrolle dependiendo del modelo causal predominante en cada época, y negando en una medida variable los planteamientos preexistentes¹². Recientemente, el progresivo aumento de las colaboraciones de investigación multidisciplinares dentro del campo de la epidemiología, junto con las novedosas

aproximaciones estadísticas multinivel, que integran variables de los niveles poblacional, individual y molecular (con especial relevancia en el desarrollo de las medicinas personalizada y de precisión), ha permitido recuperar las variables ecológicas y estudiar cómo interactúan entre sí estos tres niveles en la inferencia causal de los fenómenos de enfermedad¹³.

Dejando al margen las limitaciones metodológicas en la detección de los suicidios consumados, las llamativas diferencias de tasa de incidencia de suicidio entre países (e incluso comunidades autónomas), y las fluctuaciones en las tendencias temporales descritas desde Durkheim hasta nuestros días, sugieren que existe un potencial beneficio en identificar y tratar los factores de riesgo supraindividuales (macro-económicas, sociales, culturales, etc.) para el suicidio^{14,15}. Consideramos que, con este objetivo, es necesaria la integración del trabajo de los clínicos con el de los investigadores en “ciencias poblacionales”. El ejemplo de otros países ofrece pistas para la articulación de potenciales cambios que pueden favorecer este trabajo investigador multidisciplinar y multinivel. La alarma por el aumento de la tasa de suicidio y su impacto diferencial en algunos estratos sociales especialmente vulnerables en Estados Unidos ha facilitado diferentes iniciativas¹⁶. En 2011, se estableció la Estrategia Nacional de Prevención del Suicidio, un plan de obligado cumplimiento, entre cuyos puntos directrices se encuentra realizar cambios políticos y ambientales para potenciar la articulación entre prevenciones clínica y poblacional¹⁷. Tanto el National Institute of Mental Health (NIMH), la mayor agencia financiadora de investigación en psiquiatría, como los Centers for Disease Control (CDC), principales agentes federales para el control y la prevención de la enfermedad y la discapacidad, tienen programas específicos sobre suicidio.

El estudio de los determinantes ecológicos de la enfermedad permite encontrar dianas para la

intervención preventiva alternativas a las de las intervenciones individuales. En Europa, existen experiencias exitosas en la prevención del suicidio con intervenciones orientadas al nivel poblacional. Por ejemplo, la reducción del tamaño de las cajas de paracetamol, un medicamento altamente tóxico en sobredosis y muy accesible para la población general, asoció una menor tasa de incidencia de mortalidad por sobreingesta medicamentosa voluntaria en el Reino Unido¹⁸. Dificultar el acceso a las armas de fuego y a los puntos de concentración de suicidio por precipitación (puentes, etc.) también ha demostrado eficacia al reducir la tasa específica de suicidio por estas causas, con datos que además sugieren que el exceso de riesgo evitado no se transmite a otros puntos de precipitación ni a otros métodos de suicidio¹⁹. En nuestro país, no tenemos grandes ejemplos de prevención de las conductas suicidas con medidas orientadas al nivel poblacional. Sin embargo, España sí tiene una tradición de abordaje de los fenómenos de enfermedad a través de intervenciones orientadas al nivel poblacional en otros ámbitos. La legislación del uso de tabaco en lugares públicos, que regula la exposición al humo de fumadores en diferentes ámbitos (incluidos los sanitarios y educativos, aspectos en los que fue pionera a nivel mundial) ha demostrado eficacia al reducir dicha exposición y sus enfermedades asociadas^{20,21}. La mortalidad por accidentes de tráfico (antes la primera causa de mortalidad por causa externa en nuestro país, primer puesto que ahora ocupa el suicidio) se ha reducido de 11,6 fallecidos diarios en 2000 a 3,2 en 2016, una reducción en la que diferentes medidas orientadas al nivel poblacional (mejoría de la red de carreteras, cambios legislativos) han tenido un papel protagonista²¹. Creemos que nuestro país es un entorno privilegiado para la adopción de estrategias ecológicas para la prevención del suicidio.

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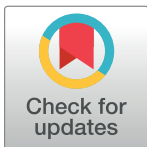
RESEARCH ARTICLE

The impact of dementia on hospital outcomes for elderly patients with sepsis: A population-based study

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Abstract

Background

Prior studies have suggested that dementia adversely influences clinical outcomes and increases resource utilization in patients hospitalized for acute diseases. However, there is limited population-data information on the impact of dementia among elderly hospitalized patients with sepsis.

Methods

From the 2009–2011 National Hospital Discharge Database we identified hospitalizations in adults aged ≥ 65 years. Using ICD9-CM codes, we selected sepsis cases, divided them into two cohorts (with and without dementia) and compared both groups with respect to organ dysfunction, in-hospital mortality and the use of hospital resources. We estimated the impact of dementia on these primary endpoints through multivariate regression models.

Results

Of the 148 293 episodes of sepsis identified, 16 829 (11.3%) had diagnoses of dementia. Compared to their dementia-free counterparts, they were more predominantly female and older, had a lower burden of comorbidities and were more frequently admitted due to a principal diagnosis of sepsis. The dementia cohort showed a lower risk of organ dysfunction (adjusted OR: 0.84, 95% Confidence Interval [CI]: 0.81, 0.87) but higher in-hospital mortality (adjusted OR: 1.32, 95% [CI]: 1.27, 1.37). The impact of dementia on mortality was higher in the cases of younger age, without comorbidities and without organ dysfunction. The cases with dementia also had a lower length of stay (-3.87 days, 95% [CI]: -4.21, -3.54) and lower mean hospital costs (-3040€, 95% [CI]: -3279, -2800).

Conclusions

This nationwide population-based study shows that dementia is present in a substantial proportion of adults ≥ 65 s hospitalized with sepsis, and while the condition does seem to come

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Data Availability Statement: The data come from anonymized registries and, according to Spanish law, are exempt from the necessity for informed consent. As a result of the confidentiality agreement signed with the Ministry of Health, Social Services and Equality, the data from this study cannot be shared with third parties. Should any researcher wish to gain access to these data, they can do so by applying directly to the Ministry through the following link: https://www.msssi.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/SolicitudCMBDDocs/Formulario_

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with a lower risk of organ dysfunction, it exerts a negative influence on in-hospital mortality and acts as an independent mortality predictor. Furthermore, it is significantly associated with shorter length of stay and lower hospital costs.

Introduction

Dementia is a global public health matter that affects 44 million people worldwide and costs 1% of global GDP [1]. It is estimated that the number affected will double in the next few years as a result of an ageing population and the lack of effective available options for prevention [2, 3]. Previous studies have shown that the prevalence of dementia among hospitalized patients is high [4–8], and on the rise [5,6]. In addition, various studies have highlighted that dementia increases the risk of death in elderly patients hospitalized for acute diseases [5, 6, 9] as well as hospital stays and costs [4, 6, 7, 10].

A large proportion of hospitalizations of patients with dementia are related with infectious processes and sepsis [5, 6, 8, 9, 11, 12]. In fact, sepsis is increasing in the elderly [13] and it is recognised as a global health priority [14] due to its high morbidity, mortality and utilization of hospital resources, especially when it presents with organ dysfunction [15]. Nevertheless, there is limited population-data information on the impact of dementia among elderly hospitalized patients with sepsis. Recently, a retrospective population-based study carried out in Taiwan [16] found that dementia increased the risk of organ failure and therefore mortality in hospitalized older adults. However, this study did not specifically analyse the characteristics or outcomes of the patients with sepsis, and for that reason it is difficult to understand the impact of dementia on the outcomes in elderly hospitalized patients with sepsis.

Spain is one of the countries with the highest prevalence of dementia worldwide [3] and this study aims to analyse the epidemiological characteristics and the impact of dementia on organ failure, in-hospital mortality and the utilization of hospital resources by adults aged ≥ 65 years with sepsis via the Spanish national database of hospital discharges. Our hypothesis is that patients with dementia have a higher risk of acute organ dysfunction, greater rates of in-hospital mortality and use more hospital resources.

Materials and methods

Design and data source

The data used come from the official database (CMBD) of the Spanish National Health System (Ministry of Health, Social Services and Equality). According to the regulations of the Spanish National Health System, every health professional should enter—at the moment of each patient's hospital discharge—all of the diagnoses and procedures carried out, using the 9th revision of the International Classification of Diseases (ICD-9-CM) and the associated “diagnosis-related groups” or DRGs. This information, the completion of which is a legal requirement, is gathered together in a national database called the “Minimum Basic Data Set” (*Conjunto Mínimo Básico de Datos*, CMBD), which includes more than 97% of the hospital discharges that occur in Spain each year, and is considered representative of the national population [17]. In the CMBD each hospitalization is treated as a specific record, and includes demographic information, type of admission, dates of admission and discharge, destination on discharge, primary diagnosis, 13 secondary diagnoses and up to 20 procedures carried out during the hospitalization [17–18].

Population studied. Identification of cases and definitions

We included hospitalizations of ≥ 65 s with sepsis from January 1st 2009 to 31 December 2011. In order to identify sepsis, previously used codes to define infection were employed [19–21]: 038 (038.0, streptococcal septicaemia; 038.1, staphylococcal septicaemia; 038.2, pneumococcal septicaemia; 038.3, septicaemia due to anaerobes; 038.4, septicaemia due to other Gram-negative organisms; 038.8, other specified septicaemias; 038.9, unspecified septicaemia); 003.1 (*Salmonella* septicaemia); 020.2 (septicaemic plague); 036.2 (meningococcal septicaemia); 036.3 (Waterhouse–Friderichsen syndrome); 054.5 (herpetic septicaemia); 098.89 (gonococcaemia); 112.5 (systemic candidiasis); 112.81 (candida endocarditis); 117.9 (other and unspecified mycoses); and 790.7 (bacteraemia). The ICD-9-CM code for sepsis, 995.91 (sepsis, systemic inflammatory response syndrome due to infectious process without organ dysfunction), which was introduced in Spain in January 2004, was also included [17].

To identify cases with acute organ dysfunction, we used ICD-9-CM code 995.92 (severe sepsis, sepsis with organ dysfunction)—as well as the codes that specifically define organ dysfunction. These specific codes were [19,20]: respiratory: 518.81 (acute respiratory failure), 518.82 (other pulmonary insufficiency), 518.84 (acute on chronic respiratory failure), 518.85 (acute respiratory distress syndrome after shock or trauma), 786.09 (respiratory distress, insufficiency), 799.1 (respiratory arrest), 96.7 with all sub-codes (invasive mechanical ventilation); cardiovascular: 785.5 with all sub-codes (shock without mention of trauma, includes 785.51, 785.52, 785.59), 458 (hypotension, 458.0, 458.8 458.9), 796.3 (nonspecific low blood pressure reading); renal: 584 with all sub-codes (acute renal failure), 580 (acute glomerulonephritis), 39.95 (haemodialysis); hepatic: 570 (acute and subacute necrosis of liver), 572.2 (hepatic coma), 573.3 (hepatitis, unspecified); hematologic: 286.6 (defibrination syndrome), 286.9 (other and unspecified coagulation defects), 287.3–5 (secondary thrombocytopenia, unspecified); neurologic: 293 (Transient organic psychotic conditions), 348.1 (anoxic brain damage), 348.3 (encephalopathy, unspecified), 357.82 (critical illness polyneuropathy), 780.01 (coma), 780.09 (drowsiness, unconsciousness, stupor), 89.14 (electroencephalogram) and metabolic: 276.2 (acidosis, metabolic or lactic).

This combination of codes from the ICD-9CM has shown capable of accurately estimating the burden of sepsis and organ dysfunction [21], and has been used previously by our research group [22]. Dementia cases were identified by the presence, in the principal or secondary diagnoses, of the following ICD-9CM codes: 290 (dementias), 294.1 (dementia in conditions classified elsewhere), 294.2 (dementia, unspecified), 331.0 (Alzheimer's disease), 331.1 (frontotemporal dementia), 331.2 (senile degeneration of brain), 331.82 (dementia with Lewy bodies) [4,7]. The cases with and without dementia were compared in relation to the primary variables of interest—including the presence of organ failure, in-hospital mortality, and hospital resource utilization (length-of-stay and cost). These variables were also examined according to age, given its influence on patients' outcomes and the use of resources in septic patients [13]. Likewise, we analysed other demographic characteristics, such as sex or institutionalization status (whether the subject lived in a nursing home before hospitalization), as well as other covariates of clinical importance like the burden of comorbidities, the potential site of infection, microbiological data and whether invasive life-support procedures were used. These procedures were defined as: infusion of vasopressor agent (ICD-9CM code: 00.17); continuous invasive mechanical ventilation (ICD-9CM code: 96.70, 71 y 72); and haemodialysis (ICD-9CM: 39.95). In order to explore comorbidity, we used the Charlson Index in the version validated by Deyo for use on administrative databases [23] and improved for ICD-9CM [24] for the 14 diagnosis fields. This index includes specific comorbid conditions of known prognostic value, which are classified using ICD-9 codes from prior outpatient and inpatient codes.

Previous epidemiological studies have shown its usefulness in assessing risk of death in septic patients [25]. For the purposes of this study, the presence of dementia in the Charlson Index was excluded [12, 16]. To be able to identify specific microorganisms, we used code 041, which, according to the ICD-9-CM coding manual, is used as an additional code to identify the bacterial agent in diseases classified elsewhere [17].

Ethics

The data are anonymized and, according to Spanish law, are exempt from the necessity for informed consent [26]. They come from hospital discharge records collected and de-identified by the Spanish Ministry of Health, Social Services and Equality. The authors requested and obtained access to the data from the Ministry and, due to a signed confidential agreement under the project PI09/0597, cannot share these data with third parties. However, these records are publicly available for research purposes. Requests of access to the data should be addressed directly to the Ministry [27].

Analysis of data

We carried out descriptive and comparative analyses of the cases with and without dementia, including clinical and demographic data, the burden of comorbidities, the presence of organ failure, in-hospital mortality, length-of-stay and hospital costs. The Charlson Index was calculated—using the improved version of Stata 14—and expressed as a continuous variable and, in addition, as a category in 4 groups (0, 1–2, 3–4, >4) of increasing severity and impact on outcomes [28]. Case Fatality Rate (CFR) was calculated as the number of deaths divided by the number of cases and expressed as a percentage. The quantitative variables are presented as means with standard deviations, and the categories as overall counts and percentages. The association between qualitative variables was analyzed via the Pearson χ^2 test or Fisher's exact test. A t-test was used to compare continuous variables.

The specific effect of dementia on the primary endpoints was calculated using multivariate regression models. In order to evaluate the effect on organ dysfunction we used two different adjusted logistic regression models: Model 1 included the main baseline characteristics: sex, age and the burden of comorbidities, whereas Model 2 also included the identification of the pathogen and the site of infection.

Regarding in-hospital mortality, before carrying out the multivariate analysis, we performed an exploratory analysis, calculating the independent effect of dementia on each of the principal covariates (sex, age, comorbidities, identification of pathogens, site of infection, and presence of organ dysfunction). Following this, we used adjusted logistic-regression techniques on three models, which included Models 1 and 2 and an additional third model that included the presence of organ failure.

For the continuous variables relating to hospital resources (length-of-stay and costs), we employed multivariate linear-regression models, adjusted by two further models: Model 4, included baseline characteristics, identification of pathogen and site of infection, and presence of organ dysfunction; Model 5 added invasive therapeutic measures to the variables in Model 4.

The results of logistic regression models are presented as odds ratios (ORs) with 95% confidence intervals (95%CI), and those of the linear regression models as coefficients (β), also with 95% confidence intervals. The statistical analysis was carried out using STATA 14 (1985–2015 StataCorp LP. TX 77845 USA). Results were considered significant with a p-value <0.05.

Results

In the period analyzed, there were 148 293 entries with sepsis in adults aged ≥ 65 years, of which 16 829 cases (11.3%) had a diagnosis of dementia. Around 45.8% of cases ($n = 7712$) were coded as Alzheimer's disease, 18.5% ($n = 3119$) as vascular dementia and the remaining 35.6% ($n = 5998$) was made up of mixed dementias and other types of dementia.

Clinical and demographic characteristics

As shown in [Table 1](#), the cohort with dementia showed a clear predominance of women and a greater mean age—more than half of the cases were 80 or over, while 54% of the cases without dementia were under that age. Although in both groups hospital admission was primarily non-elective through emergency departments, there were differences between groups, and planned admission was significantly lower in cases with dementia.

Before hospital admission, 11.9% of the cases with dementia were institutionalized compared to 3.1% of those without dementia.

Likewise, while the reasons for admission were primarily medical in both groups, the percentage of surgical cases was significantly lower in the cohort with dementia, with 5% of cases. Sepsis was the cause of admission for 62% of cases with dementia, and 43% of the cohort without dementia; being the differences statistically significant.

In [Table 1](#), the values from the Charlson Index show that the cohort with dementia had a significantly lower burden of comorbidities than the cohort without dementia. In addition, except for diabetes and cerebrovascular diseases, the frequency of specific comorbidities was significantly lower in the cohort with dementia.

The most frequent potential sources of sepsis were genitourinary, being the percentage of cases significantly greater in the cohort with dementia (40% vs. 29%) and respiratory (18% vs. 17.3%). However, both the identification of pathogens (42.6% vs. 54.1%) and the presence of bacteraemia (18.2% vs. 29.4%) were significantly lower in the cohort with dementia. In both cohorts the most frequent pathogen identified was gram-negative bacteria.

Organ dysfunction

As shown in [Table 1](#), almost 40% of cases overall were not suffering from organ dysfunction with a slightly—but significantly—larger proportion being found in the cohort with dementia. Furthermore, the percentage of dementia cases who presented with a single dysfunction was greater (35.5% vs. 30.1%), while this relationship was inverted in those cases with dysfunction of two or more organs.

Similar differences can be observed in [Table 2](#) for the specific dysfunctions analyzed, and the cohort with dementia showed a significantly lower frequency for each. In both cohorts respiratory dysfunction was the most common, followed by kidney dysfunction and then cardiovascular, whose occurrence was notably different between cohorts.

[Table 2](#) also presents the results of the multivariate analysis in which the impact of dementia on the presence and type of organ dysfunction was analyzed. The first model was adjusted for age, sex and points on the Charlson Index; the second, additionally adjusted for the site of infection and identification of pathogens. After adjustment, in Model 1, dementia was associated with 7% lower risk of presenting with organ dysfunction than the cohort without dementia. Meanwhile, in Model 2, this difference increased to 16%. In the individual analyses of the individual types of dysfunction, in all of them and in both models, dementia was associated with a significantly lower risk.

Table 1. General characteristics of the population 2009–2011.

	With dementia	Without dementia	p-value
	16 829 (11.3)	131 464 (88.7)	
Year of Study			0.505
2009	5244 (11.3)	41 360 (88.7)	
2010	5551 (11.3)	43 556 (88.7)	
2011	6034 (11.5)	46 548 (88.5)	
Sex			<0.001
Women	9587 (57)	57 708 (43.9)	
Age, years			<0.001
65–69	379 (2.2)	18 624 (14.2)	
70–74	1007 (6.0)	22 205 (16.9)	
75–79	2811 (16.7)	30 734 (23.4)	
80–84	4860 (28.9)	28 248 (21.5)	
85–89	4920 (29.2)	20 592 (15.7)	
≥90	2852 (17.0)	11 061 (8.4)	
Mean±SD [#]	83.6±6.3	78.7±7.7	<0.001
Type of hospital admission			<0.001
Non-elective	16 077 (95.5)	120 026 (91.3)	
Institutionalized	1995 (11.9)	4121 (3.1)	<0.001
Medical pathology	15 980 (95.0)	103 890 (79.0)	<0.001
Sepsis as reason for admission	10 391 (61.7)	56 778 (43.2)	<0.001
Charlson Index			<0.001
0 points	5991 (35.6)	28 506 (21.7)	
1–2 points	8330 (49.5)	61 098 (46.5)	
3–4 points	2100 (12.5)	27 986 (21.3)	
>4 points	408 (2.4)	13 874 (10.5)	
Mean±SD [#]	1.23±1.34	2.06±1.90	<0.001
Principal comorbidities			
Diabetes	4906 (29.2)	35 607 (27.1)	<0.001
Cerebrovascular disease	2657 (15.8)	11 739 (8.9)	<0.001
Chronic kidney disease	2167 (12.9)	23 121 (17.6)	<0.001
Congestive heart failure	1936 (11.5)	23 388 (17.8)	<0.001
Chronic obstructive pulmonary disease	1789 (10.6)	23 852 (18.1)	<0.001
Cancer	954 (5.7)	27 498 (20.9)	<0.001
Peripheral vascular disease	740 (4.4)	8270 (6.3)	<0.001
Acute myocardial infarction	471 (2.8)	5834 (4.4)	<0.001
Site of infection	11 248 (66.8)	94 362 (71.8)	
Genitourinary	6803 (40.4)	38 259 (29.1)	<0.001
Respiratory system	3023 (18)	22 761 (17.3)	0.036
Soft tissue	573 (3.4)	4923 (3.7)	0.028
Abdomen	359 (2.1)	9355 (7.1)	<0.001
Identification of pathogens	7160 (42.6)	71 081 (54.1)	<0.001
Gram-negative bacteria	5159 (72.0)	47 798 (67.2)	<0.001
Gram-positive bacteria	2591 (36.2)	28 660 (40.3)	<0.001
Number of organ dysfunction**			<0.001
None	6493 (38.6)	48 123 (36.6)	
1	5979 (35.5)	39 542 (30.1)	

(Continued)

Table 1. (Continued)

	With dementia	Without dementia	p-value
≥2	3391 (20.2)	39 646 (30.2)	

Chi-squared Test

Student's T-Test; SD: Standard Deviation

**in 3.4% of cases the number of organ failures was not specified.

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Among cases who presented with organ dysfunction, 3.6% (n = 376) in the dementia cohort and 25.5% (n = 21 280) in the without dementia cohort received invasive therapeutic measures for organ-system support; the difference was statistically significant (p<0.001).

Mortality

The CFR was 43% (n = 7276) in the cohort with dementia and 34% (n = 45 187) in the non-dementia cases, and these differences were statistically significant.

In both cohorts (see Fig 1), to be a woman, of more advanced age, with a greater burden of comorbidities, the non-identification of the site of infection or the pathogen, and the presence of organ dysfunction were all associated with higher mortality. Nevertheless, as it can be seen, there was a significant difference in mortality between cohorts, with higher values for the dementia cohort in all of the variables analyzed.

The same chart shows the effect of dementia on mortality, adjusted for each of the variables. These results indicate that dementia independently augments the mortality risk for each variable analyzed, while the extent of the effect is greater in specific groups, namely: the younger patients with less comorbidities and organ dysfunction. Thus, adjusting for age, the mortality of cases with dementia is 26% higher than cases without dementia. For subjects between 65 and 69 years old, the OR of death is 1.51 times higher in the patients with dementia, while it decreases to 1.12 times for those ≥90. The same occurs with the Charlson Index, where the impact of dementia on mortality shows an OR of 1.71 in cases without comorbidity and of 1.42 where there is a higher burden of comorbidities. Having analyzed organ dysfunction, the results of the analysis indicate that in cases without organ dysfunction the risk of death is twice as high in patients with dementia, while said risk is 43% higher in cases with organ dysfunction.

As regards the utilization of therapeutic measures for organ-system support, although they are used in 86% fewer cases in the cohort with dementia. In those cases where these measures

Table 2. Effects of dementia on acute organ dysfunction in patients with sepsis.

	With dementia Cases (%)	Without dementia Cases (%)	Model 1 OR (95%CI)	Model 2 OR (95% CI)
Acute organ dysfunction	10 336 (61.4)	83 341 (63.4)	0.93 (0.90, 0.97)	0.84 (0.81, 0.87)
Respiratory	4190 (24.9)	38 362 (29.2)	0.85 (0.82, 0.89)	0.80 (0.77, 0.83)
Cardiovascular	3329 (19.8)	37 089 (28.2)	0.67 (0.64, 0.70)	0.59 (0.57, 0.62)
Renal	3957 (23.5)	39 431 (30.0)	0.75 (0.72, 0.78)	0.71 (0.69, 0.75)
Hepatic	164 (1.0)	3411 (2.6)	0.64 (0.55, 0.76)	0.61 (0.52, 0.72)
Hematological	523 (3.1)	8804 (6.7)	0.48 (0.44, 0.53)	0.46 (0.42, 0.51)
Metabolic	645 (3.8)	7823 (6.0)	0.61 (0.56, 0.66)	0.56 (0.51, 0.61)
Neurological	1033 (6.1)	9137 (7.0)	0.85 (0.80, 0.91)	0.85 (0.79, 0.91)

Model 1: adjusted for sex, age and points on the Charlson Index

Model 2: adjusted for sex, age, points on the Charlson Index, identification of pathogens and site of infection

<https://doi.org/10.1371/journal.pone.0212196.t002>

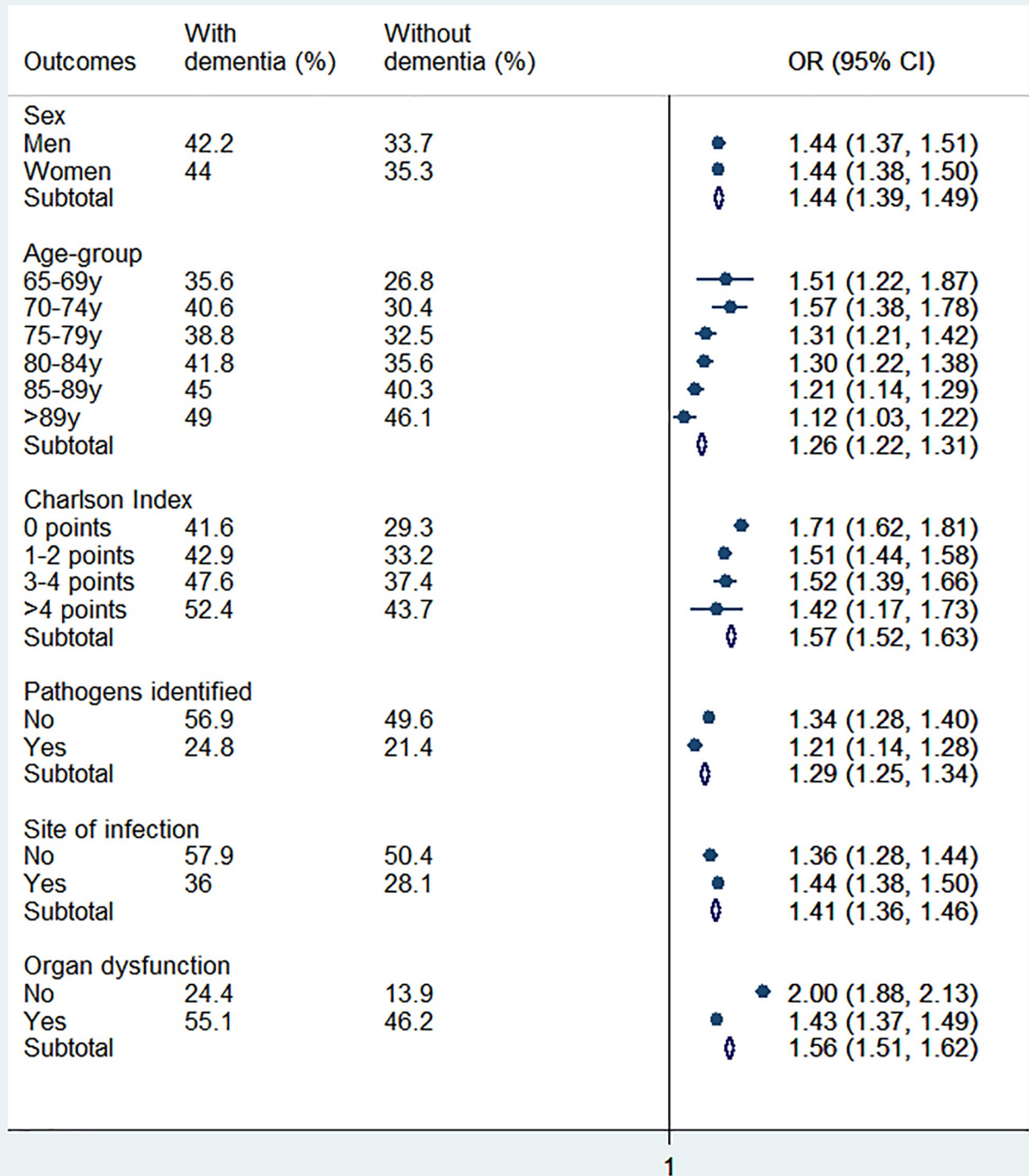


Fig 1. Likelihood of in-hospital mortality from principal covariates in dementia cases compared with non-dementia cases.

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are employed, we did not observe significant differences in the mortality of the two groups (OR:0.89, 0.72–1.09).

In Table 3, the results of the multivariate regression analysis show the impact of dementia on in-hospital mortality. The cohort with dementia presents a risk of death 36% higher than the cohort without dementia, controlled for baseline covariables (Model 1). Nevertheless, this risk is reduced to 23% if the detection of pathogens and the potential site of infection are controlled for (Model 2), and to 32% when the presence of organ dysfunction is also controlled for.

Utilization of resources

Both the average length-of-stay and the mean hospital costs were significantly lower in the cohort with dementia. The mean stay was 11.3 days for the cohort with dementia and 17.4 days for the without dementia cases. These differences are maintained when analyzing the cases who died as well as those who survived their stay. For cases who died the mean stay was 8.6 days in the cohort with dementia, against 14.7 days in the cohort without dementia. As shown in Fig 2, the mean length-of-stay decreases with increased age, but the decline is clearly less pronounced in the cohort without dementia and the differences between both groups are much more marked between 65 and 85 years of age.

As regards the costs, Table 4 shows a mean hospitalization cost of €6824 in the cohort with dementia and €11,230 for cases without dementia. Fig 3 shows the mean costs for both cohorts, as related to age and status on discharge; in the same figure we can see that—for the without dementia cases—the mean costs are much greater in cases where the patient died than in those that survived their hospital stay, and that in both cases the figure falls with increased age. In cases with dementia the cost is practically stable for both living and dead in the different age ranges. The curves of both cohorts show a substantial difference between 65 and 80 years of age, and tend to overlap from 90 onwards.

The results of the multivariate linear regression model employed to evaluate the impact of dementia on the utilization of hospital resources is shown in Table 4. This analysis, adjusted for age, sex, points on the Charlson Index and the presence or non-presence of organ dysfunction, indicates that dementia involves a 3.87-day reduction in length of hospital stay. This difference is reduced to -2.69 days if adjustment for the use of invasive therapeutic measures is accounted for. The difference in mean hospital costs per case is €3040 lower (95%CI: -3279, -2800) in patients with dementia, but this is reduced to -1489 euros (95%CI: -1713, -1266) when invasive therapeutic measures for life support are incorporated into the model.

Discussion

This nationwide population-based study shows that dementia is present in a substantial proportion of adults ≥65s hospitalized with sepsis, and while the condition associates with a lower

Table 3. Impact of dementia on in-hospital mortality.

	With dementia (%)	Without dementia (%)	Adjusted OR (95%CI)		
			Model 1	Model 2	Model 3
Mortality	43.2%	34.4%	1.36 (1.32, 1.41)	1.23 (1.19, 1.27)	1.32 (1.27, 1.37)

Model 1: adjusted for sex, age and points on the Charlson Index

Model 2: adjusted for sex, age, points on the Charlson Index, identification of pathogens and site of infection

Model 3: adjusted for sex, age, points on the Charlson Index, identification of pathogens and site of infection and presence of organ dysfunction

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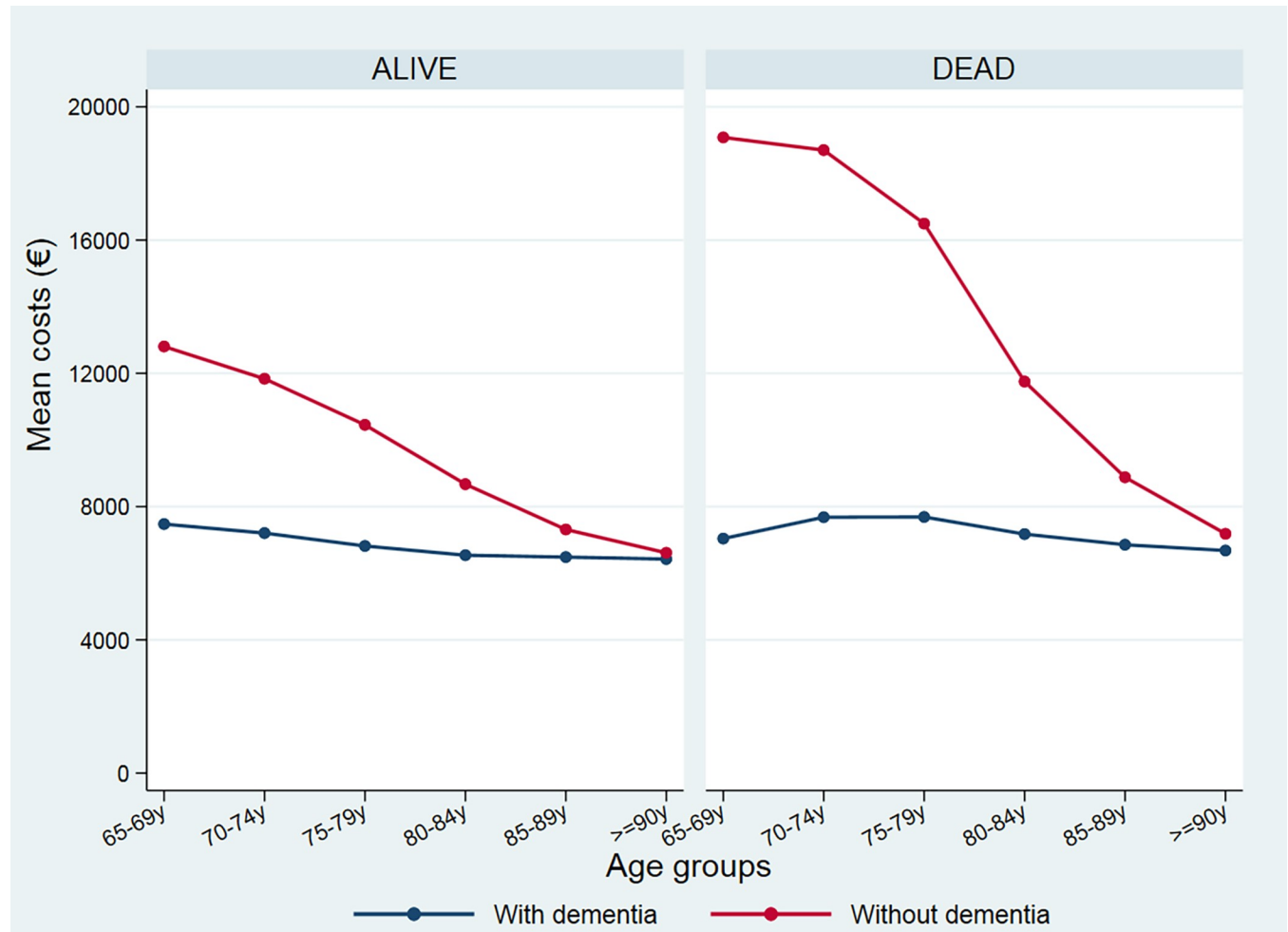


Fig 2. Mean length-of-stay for patients with and without dementia by age and vital status on discharge.

<https://doi.org/10.1371/journal.pone.0212196.g002>

risk of organ dysfunction, it exerts a negative impact on in-hospital mortality and acts as an independent mortality predictor. The negative impact of dementia on mortality is greater in lower age-groups, groups with a lower comorbidity burden and in cases without organ dysfunction. Furthermore, it is significantly associated with shorter length of stay and lower hospital costs.

As far as we know, this is the first population-level study which investigates the epidemiology and outcomes of hospitalized patients with sepsis and dementia. Our data shows that

Table 4. Impact of dementia on utilization of hospital resources.

Hospital Resources	With dementia	Without dementia	Adjusted (95%CI)	
			Model 4	Model 5
Length-of-stay, mean number of days	11.3±12.4	17.4±21.4	-3.87 (-4.21,-3.54)	-2.69 (-3.02, -2.36)
Costs, € mean	6824±4260	11 230±15 793	-3040 (-3279, -2800)	-1489 (-1713, -1266)

Model 4: adjusted for sex, age, Charlson Index, and presence of organ dysfunction

Model 5: adjusted for sex, age, Charlson Index, presence of organ dysfunction, and invasive therapeutic measures

<https://doi.org/10.1371/journal.pone.0212196.t004>

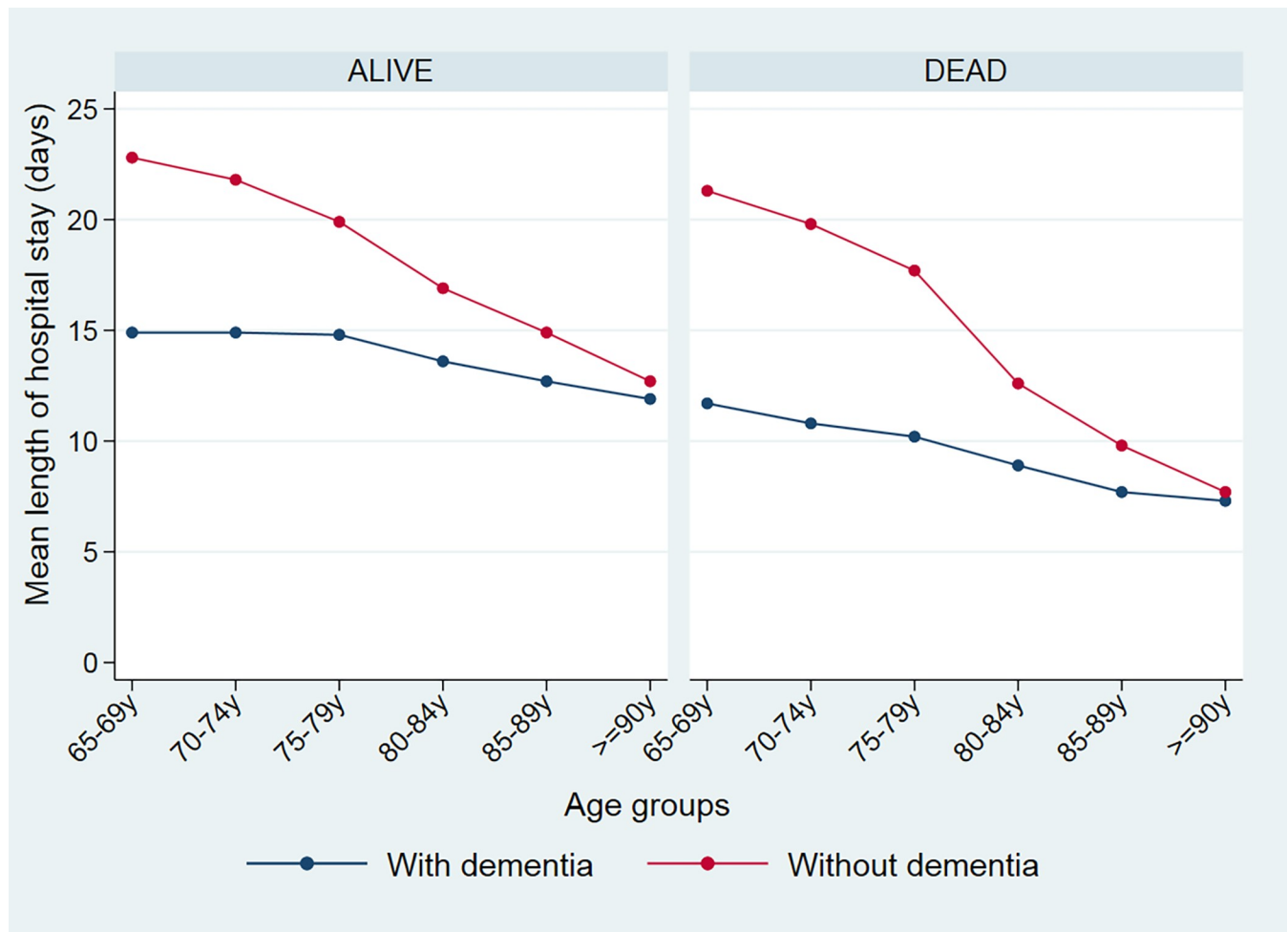


Fig 3. Mean hospital costs for patients with and without dementia by age and vital status on discharge.

<https://doi.org/10.1371/journal.pone.0212196.g003>

dementia is common in the adult population ≥ 65 with sepsis—affecting 11.3%, with a distribution that increases progressively with age and that more than half of the cases are women. These findings are in line with the literature, although the observed frequency is somewhat higher than that referred to in studies which analyze its prevalence in the general hospital population [6, 7, 12, 29, 30]. Also, Alzheimer’s disease is common and represents almost half of the cases with dementia [29, 31–33]. It is important to highlight that in 62% of cases with dementia, sepsis was the reason for hospital admission. This figure, significantly higher than that for cases without dementia, suggests a community-acquired origin of sepsis in a large proportion of those patients. In line with literature, the most frequent site of infection was urinary followed by respiratory [4, 5, 8, 12].

Several studies have demonstrated that mortality from sepsis is associated with greater age, greater burden of comorbidities and, in particular, with the presence of organ dysfunction [13, 15, 19–22]. The results of our study accord with these previous studies, in addition to showing that the existence of dementia is an independent factor associated with higher mortality in this population.

In this study, the cohort with dementia presents a lower burden of comorbidity as evaluated through the Charlson Index, which does in fact contrast with some previous publications [7,

12, 34], but agrees with others [6, 30, 33]. Although we cannot discount that patients with dementia are subject to under-diagnosis of comorbidities, the presence of a profile with higher diabetes and cerebrovascular-disease prevalence agrees with the results of prior studies [6, 30, 35, 36] and suggests that the coding is not systematically biased.

Moreover, the cases with dementia showed a significantly lower risk of acute organ dysfunction than those without dementia, after adjusting—in the multivariate analysis—for demographic and clinical characteristics known as predictive factors for outcome such as age, sex, burden of comorbidity, the identification of a potential site of infection and the responsible microorganism. Our findings contrast with those described by Shen et al. in Taiwan [16] where dementia was associated with a higher risk of organ dysfunction. This discrepancy might be due to methodological and design differences between the two studies, as their population consisted of ≥ 65 years hospitalized for any cause and they did not specifically analyze cases of sepsis. This great difference and the lack of information about cases with sepsis make it impossible to adequately compare the results. That said, we have confidence in the results of our study given that it uses cases identified through well-used and validated strategies for the epidemiological analysis of sepsis and its outcomes [13, 19–22]. In addition, as the study is based upon population data whose declaration is obligatory and not subject to systematic selection bias, there is no reason to presume that the registration of organ dysfunctions would be different between cohorts. By the same token, given the universal character of our national health system we can assume that coding practices were not due to economic incentives. Unfortunately, we have not identified any other studies that analyze the outcomes of acute organ dysfunction in patients with dementia and sepsis with which we might compare our data.

In relation to age, for patients with dementia and sepsis the increased risk of death with greater age is clearly lower than in the without dementia cases. In addition, although cases with dementia are, on average, around five years older than those without dementia, the greatest differences in mortality between the cohorts are found among lower age ranges. Along similar lines, the impact of dementia on mortality has a greater effect on clinically less severe groups—with fewer comorbidities and without organ dysfunction. Regrettably, the design of this study does not permit us to identify the causes of these differences, but our results suggest that dementia is a mortality risk factor whose impact is less perceptible with more advanced ages and/or greater clinical severity [16, 37].

The presence of dementia has a negative association with indicators of clinical management, like the identification of the site of infection, the pathogen responsible for causing the sepsis or the use of invasive techniques for organ support. The correct identification of the site of infection and the responsible microorganism are critical for clinical management of sepsis, as the administration of ineffective antibiotic increases mortality [15, 38, 39]. It must be acknowledged that the clinical manifestations of sepsis are variable and may be subtle in elderly patients—and that dementia presents additional challenges due to communication difficulties and poor tolerance for diagnostic procedures and other care activities. Nonetheless, the implementation of educational programmes for professionals on the diagnosis and early treatment of sepsis has improved patients outcomes and reduced mortality [40, 41]. Along the same lines, the results of this study suggest that it is necessary to undertake greater diagnostic efforts in these patients—once the identification of the potential site of infection and pathogen responsible is accomplished, the impact of dementia on in-hospital mortality should shrink markedly.

It is also important to mention that the use of withdrawing or withholding invasive life support measures may provide a partial explanation to some of our findings. The use of invasive therapeutic measures in patients with dementia is under debate—as the appropriateness of their

use and their results are far from clear [42–44] and, as stated by Richardson [42], acute care patients with dementia are treated substantially less aggressively than patients without dementia. Conversely, a recent study by Lagu in the US, however, shows that between 2001 and 2011 the utilization of invasive mechanical ventilation increased four times more in patients with dementia than in those without dementia [45]. In our study these measures were used in a small percentage of cases with dementia, but in those cases where they were used we did not observe significant differences in mortality between the two groups. This suggests that the selection criteria for the use of these measures were evaluated from the perspective of appropriate care and concurs with the findings of recent publications [16, 43, 46]. Unfortunately, our study design rendered it impossible to assess cases in which there have been decisions to forgo life-sustaining measures and we are unaware of the influence of patients' advanced directives in our study population. Further, studies investigating the frequency and quality of palliative care in critically ill patients with dementia are scarce [47]. However, the results of previous studies in which we participated show that, in our country, these decisions are taken by professionals on the basis of biomedical reasons of therapeutic futility or ineffectiveness, that their attitude tends to be conservative and less pro-active than in other countries, and that such decisions are taken in approximately 6.6%–9.8% of patients admitted to the Intensive Care Unit [48,49]. Furthermore, besides age and acute and chronic diagnoses, quality of life and functional status have the greatest impact on decisions to limit life support [48]. Accordingly, it seems eminently plausible that the presence and severity of dementia may determine less aggressive clinical management decisions and patients with dementia and sepsis may be less likely to be treated with invasive measures.

Previous studies have noted that dementia increased the mean length-of-stay and the costs of hospitalization for elderly patients diagnosed with acute conditions [5, 10]. However, our study provides contrasting results: length-of-stay and hospital costs were significantly lower for patients with dementia, both overall and when examining the cases who died or survived their hospital stay. Overall, the adjusted differences observed in our study go up to almost four days hospital stay and more than €3000 mean hospitalization costs. The lower rates of organ dysfunction and the lower use of life-support invasive measures in the dementia cohort as compared to dementia-free cases, may explain these findings. Additionally, even if in the multivariate model the adjusted size of the difference between the two groups—for both length-of-stay and costs incurred—was reduced when the use of invasive therapeutic measures was introduced as a covariate, notable differences remained. Interestingly, Lagu et al. [46], in their recent retrospective population-study of 65s and over, found that patients with dementia under invasive mechanical ventilation had shorter lengths-of-stay and lower hospital costs than those without dementia.

Our data also show that the differences in these estimators between the two cohorts are greater at lower ages. This is possibly because the gap between clinical attitudes for subjects with and without dementia, regarding the use of life-support invasive measures tends to narrow with the advancing age of patients—with an overall reduction in therapeutic efforts [42, 43, 46,48,49].

Our results expand the still scarce information available about the impact of dementia on elderly patients hospitalized with sepsis. This study used the nationwide official database of hospital discharges of the Spanish National Health System. Data entry into this database is mandatory by law, covers over 97 per cent of the all acute-care, public and private, hospitalizations nationwide and is subjected to regular audits to verify the adequacy and accuracy of the coding used [17–18]. Thus, we consider that our results could be generalized. These results could be of interest for decision-makers and the planning of care resources in an increasingly

ageing society for which a greater prevalence of dementia and sepsis is foreseen in the near future.

The limitations of our study are those inherent to investigations based on retrospectively collected clinical-administrative data. Although there are national directives for the use of the ICD-9-CM coding system, this may not have been uniform across all hospitals of the national health network and we cannot rule out coding errors despite regular audits making major errors unlikely. However, we have limited the study to a spread of recent years, as it is known that the coding in Spain has improved over the last few years. A further limitation is the absence of diagnostic information about the severity of dementia [50, 51]. Accordingly, it is necessary to bear in mind that all of these are hospital cases, and it has already been demonstrated that there is an inverse relation between the severity of the dementia and the probability of being hospitalized [52]. Moreover, we lack data about other socio-demographic characteristics like risky behaviour; pharmacological treatments; economic, cultural or educational level. This impeded our ability to better characterize the pattern of this cohort and stratify the results by severity of dementia and other risk factors. Nonetheless, the inclusion of cases which covered all subjects at the population level allows us to assume that none of the groups compared were selected with systematic bias.

Lastly, our analysis does not include non-hospitalized cases. Thus, the mortality data is in-hospital mortality and prior studies have demonstrated that patients who survive a septic episode have a higher risk of death during the following months or even years [15, 53] which makes the estimates conservative.

In conclusion, this study shows that dementia is present in a significant proportion of ≥ 65 patients hospitalized with sepsis, and that while the condition does not seem to come with a higher risk of organ dysfunction, it both exerts a negative impact on hospital mortality and acts as an independent mortality predictor. According to our results this impact is higher in lower age-groups, groups with a lower comorbidity burden and in cases without organ dysfunction. In addition, it is associated with a significantly lower length of stay and hospital cost. Further study is needed into the factors associated with the negative effect of dementia in elderly patients with sepsis.

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Beyond Statistical Significance: An Underrated Suicide Prevention Intervention

To the Editor: In their recently published report of a randomized trial, Vaiva et al¹ found that suicide attempters allocated to a decision-making algorithm for suicide (ALGOS) were 26% less likely to reattempt suicide within 6 months after discharge than controls who received treatment as usual (TAU) (12.8% vs 17.2% relapses, respectively; difference between groups: 4.4%, 95% confidence interval [CI]: -0.7%, 9.0%; relative risk: 0.74; 95% CI, 0.54–1.01). Because the early postdischarge period entails exceptionally high relapse risk,² the study’s main outcome was the difference in the percentage of reattempts during the first 6 months of follow-up. The observed difference was described as “not significant” at the provided *P* value of .059 for the complete-case analysis.

We would like to warn against concluding that the intervention was not effective, given that the conflation of “statistical significance” with decision-making is error-prone.³ In addition, notwithstanding concerns about arbitrary *P* value cutpoints, 2 key aspects of the study design and analysis should be considered when interpreting the results. First, their control intervention, a priority appointment after discharge combined with a referral to an outpatient clinician for follow-up, has proven effective at lowering relapse risk after suicide attempt in comparable contexts with universal health coverage.⁴ In fact, enhancing follow-up contacts with health providers is considered the single most effective clinical intervention to reduce suicide behaviors.⁵ Comparing any intervention to a highly effective TAU can be challenging, and yet there was a difference of over 4 percentage points in suicide reattempts among those randomized to ALGOS. Second, the 2 study groups differed substantially in their loss to follow-up (13.6% in ALGOS vs 18.4% in TAU at 13 months, *P* = .038). Given that treatment engagement is a key component of suicide prevention efforts,⁶ we cannot rule out the possibility that lost individuals may have higher relapse rates than the observed individuals. If that was the case, observed data would likely underestimate ALGOS effectiveness. Despite this, all reported analyses in the study were conducted in an intention-to-treat (ITT) basis. Notably, ITT analysis tends to yield conservative effect differences between compared interventions, and, in the presence of loss to follow-up or lack of adherence (especially if it affects differentially the studied interventions, as is the case here), there is no guarantee that an ITT approach adequately estimates the clinical effectiveness of the study.⁷

Two strategies could have enhanced Vaiva and colleagues’ study report and should be considered in the future. From an analytic perspective, long-lasting trials with substantial loss to follow-up can benefit from being analyzed using several different approaches, including not only intention-to-treat, but also “as-treated” and “per-protocol” analyses, where effect estimates can be controlled by differential adherence and other potential post-randomization, time-varying confounders.^{7,8} Regarding the interpretation of results, an observed difference between study groups should be judged considering several aspects, including effect size, precision of the estimate, and features of the study design, rather than relying solely on statistical testing.^{3,9}

Suicide is a major global health concern. Suicide attempt, its more reliable risk marker, is an increasingly frequent clinical entity

that drives substantial burden for health systems and generates an enormous societal impact.¹⁰ Consequently, effective interventions aimed at lowering suicidal behaviors are a priority clinical need. Pragmatic clinical trials conducted in real clinical settings, like the study by Vaiva et al,¹ usually entail methodological challenges that can lead to dilution of the effect.¹¹ Nevertheless, results from the real world are sought after by policy makers because of their high external validity.¹¹ We believe that, by estimating the effectiveness of a decision-making algorithm that improves clinicians’ ability to support people at high risk of suicide attempt, Vaiva et al are contributing valuably to suicide prevention.

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Dr Berrouiguet and Colleagues Reply

To the Editor: We thank Martínez-Alés et al for their comments on our study¹ in which we assessed the efficiency of the ALGOS brief contact intervention (BCI). Martínez-Alés and colleagues warn against statistical misinterpretations and concluding that the intervention is not efficient. It has long been asserted that the harms of statistical testing in more uncontrollable and complex research settings (such as “real world” suicide prevention) have far outweighed its benefits. As suggested by Martínez-Alés et al, we also performed an “as treated” analysis on the same sample.² We also believe that the integration of web and smartphone technology may reinforce the efficiency of actual BCIs. Overall, these strategies could lead to dynamic monitoring of the risk assessment, leading to real-time, personalized interventions.³

Beyond the efforts to reach “statistical significance,” it is important to note that ALGOS results brought about an important change in French suicide prevention policy. After the ALGOS study was published, Duhem et al⁴ proposed assessing the efficiency of the algorithm as standard care for suicide attempters in 5 regions of France with different sociodemographic characteristics; this program is called Vigilans. The French Health Authority is currently supporting the establishment of Vigilans as a standard of care for all suicide attempters attended in emergency departments. Vigilans includes a multimodal suicide prevention program with long-term BCIs and crisis management. Furthermore, the program establishes a network of professionals working with different populations and in differing infrastructural conditions, which provides strong support for suicide prevention literacy in both care workers and at-risk populations. As affirmed by Martínez-Alés et al, we believe that these efforts based on an “inconclusive” randomized controlled trial will have important benefits for suicide

outcomes in France and provide an easily reproducible, efficient suicide prevention strategy.

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Fatal and Non-fatal Self-Injury in the USA: Critical Review of Current Trends and Innovations in Prevention

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Abstract

Purpose of Review To examine current trends in suicide and self-injury in the USA, as well as potential contributors to their change over time, and to reflect on innovations in prevention and intervention that can guide policies and programs to reduce the burden of suicide and self-injury in the USA.

Recent Findings Suicide and non-fatal self-injury are on the rise in the USA. Reasons for such trends over time remain speculative, although they seem linked to coincident increases in mood disorders and drug use and overdose. Promising innovative prevention and intervention programs that engage new technologies, such as machine learning-derived prediction tools and computerized ecologic momentary assessments, are currently in development and require additional evidence.

Summary Recent increases in fatal and non-fatal self-harm in the USA raise questions about the causes, interventions, and preventive measures that should be taken. Most innovative prevention efforts target individuals seeking to improve risk prediction and access to evidence-based care. However, as Durkheim pointed out over 100 years ago, suicide rates vary enormously between societal groups, suggesting that certain causal factors of suicide act and, hence, should be targeted at an ecological level. In the next generation of suicide research, it is critical to examine factors beyond the proximal and clinical to allow for a reimagining of prevention that is life course and socially focused.

Keywords Suicide prevention · Suicide prediction · Machine learning · Ecologic momentary assessment · Brief contact interventions · Multilevel epidemiology

Introduction

Suicide continues to be a central contributor to lives lost across the globe and among the most common causes of death, especially in young adults. The sequelae of suicide for families and communities reverberate in grief, stigma, and increases in psychiatric conditions. The present paper outlines current trends in suicide and self-injury in the USA, as well as hypotheses and evidence regarding contributors to changes over time in the suicide rate. Further, we examine

evidence for innovations in prevention and intervention that can guide policies and programs to reduce the burden of suicide and self-injury in the USA.

Trends in Suicide and Non-fatal Self-Injury Among Adolescents and Adults

Suicide rates in the USA were generally declining among most age groups of adults throughout the late 1980s and 1990s [1]. However, since 1999, suicide rates began to increase in almost all states and in almost every age group. Analyses from the CDC indicate that from 1999 to 2016, suicides significantly increased in 44 of 50 US states and that the rate of increase was heterogeneous by location and demographics [2]. For example, suicide increased by more than 30% in 25 states, with the highest increase in suicide occurring in North Dakota (an increase of 57.6%). However, states such as Nevada, which already had the highest rates of suicide in the country, did not observe a significant increase [2]. Trends

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towards increased suicide rates continued in 2017 [3], as the overall suicide rate in the USA increased from 13.5 per 100,000 to 14.0 per 100,000.

While the rate of suicide is increasing across all age and gender groups, there have been particularly high absolute increases in suicide among men aged 45 to 64 (<https://www.cdc.gov/nchs/data/databriefs/db241.pdf>). Relative increases in suicide are greatest among those at young ages, due in part to a lower overall base rate. For example, the suicide rate among girls aged 10–14, among whom the suicide rate was 0.5 per 100,000 in 1999, tripled by 2016 [4••]. Suicide is currently the second leading cause of death among those aged 10–14, 15–24, and 25–34, with unintentional injury being the leading cause of death, indicative of the contribution of both unintentional injury and suicide to the declining life expectancy in the USA, given the young age of decedents (<https://www.nimh.nih.gov/health/statistics/suicide.shtml>).

Available evidence indicates that regions of the USA with high suicide rates and high correlation among suicides per geographic area are those with high elevation [5], as well as those with high concentrations of demographic groups at risk of suicide such as those with indigenous populations (<https://www.cdc.gov/mmwr/volumes/67/wr/mm6708a1.htm>). Further, the strength of correlation among suicides in particular geographic areas over time is also increasing, suggesting that as suicides become more common, the overall size of areas with particular high suicide rates is also increasing [6]. Occupational exposures also influence suicide: the risk is markedly salient among members of the US military, especially those exposed to active combat and traumatic events in the field [7]. While members of the military historically had lower death rates than the general population, including suicide, death by suicide increased among US army members beginning in 2004 [8], and rates are now approximately equal to the general population, due to the unprecedented increases among both civilians and military members [9].

The increasing trends in completed suicide lead to the question of whether there are increases in non-fatal self-injury as well, or whether the trends reflect rather lethality of attempts. Available data indicate that non-fatal self-injury is also increasing in the USA across age. Olfson et al. examined self-reported suicide attempts across two cross-sectional surveys of adults completed 10 years apart with similar sampling frames and measures and found modest increases in the rate of self-reported attempted suicide, from 0.62% in 2001–2001 to 0.79% in 2012–2013 [10••]. Across demographic and clinical groups, those with the highest increases included young adults aged 21–34, those with high school or less education, and those with psychiatric disorders. Hospital-treated self-harm events increased from 5.1 to 7.1 per 10,000 population from 2001 to 2011 among middle-aged individuals, an increase larger than any other age group [11]. Other

analyses of hospitalization data also demonstrate increasing trends in self-injury [12–14].

Non-fatal self-injury is increasing among youth. The prevalence of adolescents reporting that they “seriously considered attempting suicide” in the past 12 months in the USA increased from 14.5% in 2009 to 17.2% in 2017, an increase that was statistically significant (https://www.cdc.gov/healthyyouth/data/yrbs/pdf/trends/2017_suicide_trend_yrbs.pdf). However, it should be noted that overall trends since the mid-1990s suggest declines (e.g., prevalence was 29% in 1991). Emergency department visits and inpatient hospitalizations coded for suicidal ideation or attempt across 49 children’s hospitals in the USA increased from 0.66% of all encounters in 2008 to 1.82% in 2015 [15], and significant increases were observed across age, gender, and race, with the largest increases observed for 12–14 and 15–17 year olds, girls, and non-Hispanic whites. Further, among youth less than age 18 in the USA, emergency department visits coded for suicide attempts and suicidal ideation doubled between 2007 and 2015, from 580,000 to 1.12 million, with no corresponding increase in total emergency department visits [16].

Trends in Mood Disorders Among Adolescents and Adults

Mood disorders, particularly depression, are strong risk factors for self-injury and suicide. Psychiatric autopsy studies of suicide decedents compared with living controls range in the prevalence of mood disorders, with a median estimate based on systematic review of 59% (range from 30 to 93%) [17]. Meta-analytic estimate from 3275 suicide decedents indicated a pooled prevalence of affective disorders, including depression and bipolar disorders, of 43.2% [18]. Prospective data from the Danish registry among those with contact with the health system for a psychiatric disorder found an absolute risk of suicide after first contact of 6.67% [19]. Given the increased risk of suicide associated with depressive and other affective disorders, it is also worth interrogating the evidence for recent increases in mood disorders.

Mood disorders are substantially increasing in recent years among adolescents, especially adolescent girls. Mojtabai et al. found that the prevalence of DSM-IV major depressive episodes increased from 8.7% in 2002 to 11.3% in 2014 ($P < 0.001$), with a greater increase among girls than boys [20]. Updated analyses of NSDUH through 2017 have demonstrated a continued upward trajectory of MDE among girls [21••]. Independent data sources confirm that depressive symptoms have increased among girls in national representative US studies, compared with no significant change among boys [22••]. These national studies are augmented in building the evidence by other studies among young adults, particularly those in college, among

whom data indicate that anxiety and depressive disorders are increasing across the past decade [23, 24].

The increases in the prevalence of affective disorders in general population samples among adolescents are notable given the recent history of this epidemiology. Sales of prescription medication to treat depressive and related mood disorders, among both adolescents and adults, increased substantially starting in the mid-1990s [25], as did outpatient visits to psychiatric clinics for treatment of depression [26, 27]. These increases prompted questions about whether mood disorders were increasing, or whether identification and ascertainment of cases for treatment were increasing without any change in the underlying incidence and prevalence. Available reviews and meta-analyses published in the mid-2000s found no evidence for increasing incidence and prevalence of mood disorders in the community when prospective studies were analyzed [28, 29]. These reviews, however, were published before the recent, cross-study-consistent increases in mood disorders in general population samples, which began around 2010, suggesting that a new evidence base is needed as we enter a new era of mood disorders among US adolescents.

Evidence regarding changes in affective disorders among adults is more mixed, but suggested sustained increases are occurring predominately among those with low socioeconomic status. Case and Deaton found that among middle-aged men with low education, the prevalence of non-specific psychological distress has been historically increasing from 1997–1999 to 2011–2013 [30]. Goldman et al. documented that life satisfaction, positive affect, and psychological well-being decreased from 2011 to 2014 compared with 1995–1996, and negative affect increased, but only for those who are socio-economically disadvantaged [31]. National survey data conducted annually has documented recent increases in psychological distress among adults and increases in major depressive episodes that are small in magnitude and primarily confined to young adults [21••], especially those with low levels of socio-economic status [20, 21••, 32]. These results are supported by other national data also documenting increases in moderate and severe depressive episodes, primarily among those with the lowest levels of education [33]. The range of increases is small, between 1 and 3 percentage points, and inconsistent across all levels of the life course, suggesting that continued surveillance is needed to determine whether these increases reflect temporary and time-limited noise in the data, or whether there is a sustained increase that may underlie changes in suicide risk in the USA.

Why Are Suicide Rates Increasing Among Adolescents and Adults?

The increases in suicide rates are occurring coincident with increases in mood and affective disorders among adolescents and,

to an extent that is less well established, among adults. The reasons that these disorders are increasing in the population, as well as other potential reasons underlying suicide death, remain speculative. Suicide rates are increasing in tandem with unintentional injury deaths more broadly particularly due to opioid overdose, which was exponentially increasing since approximately 1999 in the USA (https://www.cdc.gov/nchs/data/health_policy/AADR_drug_poisoning_involving_OA_Heroin_US_2000-2014.pdf) [34], around the same time that suicides began increasing [35••]. Opioid overdose and suicide deaths share demographic correlates such as a greater preponderance of males, indigenous populations, and those in middle age, but the trends are to some extent discordant, given that there are different demographic groups that have had the largest increase in suicide compared with opioid overdose. Yet, some mechanisms linking the two epidemics could be that opioid use disorders increase both risk of overdose and suicide; available evidence finds that suicide among medical users of opioids increases with opioids dose [36], that communities ravaged by opioid overdoses may have collective trauma and psychological distress that would increase risk of suicide [37•], and that the availability of opioids could lead to greater access to lethal means. On the last point, there is limited evidence; currently, poisoning accounts for a minority of suicides in the USA (14.7% in 2015), and a minority of those poisoning suicides involved opioids [2]. That said, the number of deaths categorized as unintentional opioid overdoses that might have been suicides is difficult to adjudicate, given that the intentionality of death can be difficult to determine, especially among those with opioid use disorders which can increase the risk of suicidality.

Some have advanced the hypothesis that the increases in suicides, as well as overdose, alcohol consumption, and deaths due to alcohol, especially among middle-aged men and those with low educations, are the outcome of a long process that has included the erosion of a middle class with job stability for low-skill work, among other economic factors that may bring meaning to the lives of the working class [2, 37]. While such hypotheses are provocative, available analyses have largely been unable to provide compelling evidence. In a working paper by Ruhm [38], known measures of county economic decline such as home prices and unemployment predicted suicide, but explained less than 1% of the variation in rates over time. Further, Masters et al. reanalyzed vital statistics data by gender, age, and birth cohort and concluded that drug overdose rates increased across a wide range of age groups, especially those in young and middle adulthood, and did not mirror trends for other “despair”-related death such as suicide, suggesting that the drivers of opioid-related deaths in the USA were factors that could influence a broad range of age groups simultaneously, but may be separate from mechanisms that increase suicide rates [39].

Suicides would also be expected to increase with increased access to lethal means. The leading method of suicide in the

USA is with a firearm, responsible for 56.6% of male suicides in 2015 and 32.1% of female suicides. Among men, suffocation is second most common with 26.1% of suicides, followed by poisoning (9.5%). Among women, poisoning is slightly more common than firearms as a means of suicide, at 33%, followed by suffocation, responsible for 25.3%. While firearms represent a plurality of suicide deaths in the USA, available data suggest that firearm ownership is decreasing in the USA, rather than increasing [40]. Further, comparing causes of suicide death between 1999–2007 and 2008–2015, while increases in suicide occurred for both firearm and suffocation suicides, the absolute and relative increase was higher for suffocation than for firearm suicides (<https://www.cdc.gov/mmwr/volumes/66/wr/mm6610a2.htm>). There is no evidence to suggest that means to suffocation are increasing in the USA; thus, increases in access to lethal means do not currently explain increases in suicide in the USA.

Innovations in Individual-Level Suicide Prevention: the *Who* and the *When* of Suicide Risk

Decades of research aimed at the identification of individuals at high risk of fatal and non-fatal self-harm have yielded an array of biological [41–43], behavioral [44], and social [45, 46] risk factors that decision-makers use, combined, for intervention purposes. However, suicide risk factor identification has contributed minimally to effective prevention efforts, and suicide risk reduction remains a largely unmet clinical need. Even the most widely used risk assessment scales, largely based on suicide risk factors, lack enough sensitivity, specificity, and predictive value to be clinically meaningful [47]: used alone, these scales are not useful to estimate an individual's future risk of suicide [48].

A well-known reason for the lack of impact of suicide risk factor identification on suicide prediction is what Hawton termed a “base-rate problem” [49••] that leads to an excess of false positives in the clinical practice: on the one hand, most accepted risk factors for suicide, such as mood and substance abuse disorders or interpersonal conflict, are highly prevalent. On the other, suicide behaviors and specially death by suicide are relatively rare events over the lifetime of those classified as high risk. As a result, most people classified as “high risk” will never die by suicide, and a considerable amount of suicides will take place among people classified as “low risk,” as proved by substantial evidence from prospective studies. In 1983, Pokorny reported that, among a cohort of 4800 veterans, only 3.7% of high-risk predictions corresponded with true positives, and more than half of suicides took place in low-risk patients [50], a finding that has been replicated several times [51–53].

Notwithstanding, psychiatrists remain entrusted to conduct suicide risk assessments in a scientifically sound manner—e.g., using risk factors and scales, a phenomenon that Undrill sees as an approach to the management of the “institutional anxiety” suicide risk generates [54]. Notably, Mulder et al. have argued that risk categorization is not only clinically futile but also potentially harmful, in that it may “confuse clinical thinking” and lead to more coercive treatment options for those labeled “high risk” and a parallel misallocation of treatment intensity for those labeled “low risk” [55].

In the recent years, substantial attention within the field of suicide prediction has shifted towards new machine learning algorithms, derived from large databases of electronic health records. Tools derived from regression trees, neural networks, and other machine learning approaches have been shown repeatedly to outperform clinicians' predictive assessments, generating new hopes in the suicide prevention field. Notable examples include Kessler and colleagues' study featuring over 50,000 American soldiers discharged after a hospitalization [56], DelPozo-Banos et al.'s study using more than 2600 suicide cases and 52,000 paired controls from the UK [57], or Simon and colleagues' study featuring 2,960,929 patients from seven American healthcare systems [58].

Critics with machine learning–derived predictive tools usually point out limitations regarding generalizability to different settings and transparency in the model developing process. The generalizability of predictions based on complex, data-driven statistical approaches tends to depend on how similar the training dataset is to the new population in terms of variable distribution—different populations often require different model calibrations. In a comprehensive review, Belsher et al. simulated the variation of the positive predictive value of a series of machine learning algorithms for suicide prediction when implemented in hypothetical populations with different suicide rates, reporting high classification accuracy but an extremely low predictive validity in most populations [59]. This finding has somewhat “deflated some of the exaggerated hopes” associated with big data analyses and machine learning statistical methods [60] and, more importantly, emphasized the need for more accurate data recording in the clinical practice, wide availability of training datasets when legally possible, and transparent sharing of the exact analytic methods used in order to enhance the recalibration of a model before implementing it in a different population [61].

Another, less explored explanation for the lack of clinical impact of suicide risk assessments is that little is known about when this risk is higher, although time-related considerations would provide key insights for intervention planning. Most consistently accepted risk factors correspond to correlates that either remain stable over time, such as gender or family history of suicide [62], or take long periods of time to establish and eventually resolve, like most psychiatric diagnoses or a disadvantaged socio-economic status [63]. However, suicide

risk factors interact over time in complex hierarchical networks that are inherently difficult to capture using solely long-term assessments of the relation between baseline characteristics and subsequent suicide. For example, while people with schizophrenia with a low premorbid life adjustment tend to show high suicide rates right after the onset of the disease, their long-term suicide risk is low, as compared with counterparts with a better premorbid adjustment [64, 65]. In order to effectively act on suicide risk, we need to better understand short-term suicide risk factors and how they vary over time.

Suicidal ideation (SI), largely targeted as a way to prevent suicide as it usually precedes suicidal behaviors [66], is probably the most important time-varying risk factor for suicide. SI includes a spectrum of different experiences that range from passive ideas of death, through structured suicidal ideation, to the urge to attempt self-harm [67]. Most studies have measured suicidal thoughts using single-time-point measures, although recent evidence shows that SI undertakes dramatic within-person variations over short periods of time [68•]. Because single-point measures, like retrospective questionnaires, fail to capture such variation, past research has yielded interestingly mixed results. For example, while Kessler et al. estimated the risk of transition as 26% from ideation to an attempt and as 72% from a plan to an attempt [66], Baca-Garcia et al. found that passive and active suicidal ideation entailed the same lifetime suicide attempt risk [69], and Lee et al. estimated that, among suicidal ideators, making an attempt was in fact more frequent than planning it [70].

New technologies provide innovative measures of time-varying real-world determinants of suicide. In particular, computerized ecologic momentary assessment (EMA) allows for data collection “in the natural contexts of daily life” [71]. This technique measures participant’s domains of interest (whether these are emotions, cognitions, or behaviors) repeatedly, usually through smartphone-delivered assessments that can follow a timely schedule, or depend on the occurrence of a predefined behavior, or using both [72, 73•]. Hence, EMA assesses exposures and outcomes in a real-time, real-world manner and can accurately characterize daily suicidal thoughts and their external and internal triggers [74]. In addition, EMA assessments are technically feasible, enhance the participants’ compliance, and do not reactivate their negative thoughts [71]. Recent studies using this technology have successfully characterized the mentioned variation in suicidal thoughts that high-risk individuals can experience over short periods of time [75] and linked it to predictors such as life challenges and inner affect state changes [76, 77].

Apart from improving our ability to accurately determine who is at risk and when is this risk higher, the potential impact of suicide prevention efforts relies greatly on the development, implementation, and scalation of effective prevention strategies. Despite remaining key knowledge gaps, certain clinical strategies are considered

effective and recommended, especially among specific subsamples of psychiatric patients with increased suicide risk [78–80]. With respect to pharmacotherapy, clozapine [81–83] and lithium [84–86] show the most promising results for preventing suicide attempts among people with schizophrenia and bipolar disorder, respectively.

Psychosocial strategies for suicide risk reduction among people at high risk often fall within two categories: interventions directed specifically towards suicide risk and interventions aimed at intensifying their contact with mental health care providers. Among the first group, several psychotherapeutic interventions have been shown to decrease the intensity and frequency of suicidal thoughts and/or behaviors, either among all people undergoing mental health struggles or when tailored for clients with specific psychiatric diagnoses [87–89]. In general, these interventions enhance the client’s ability to cope with suicidal thoughts through the acquisition and strengthening of specific strategies and skills. However, psychotherapy for suicide behaviors has been called into question when compared with more feasible programs aimed at simply enhancing contact maintenance with providers over a sustained period of time [90]. For example, in a recent RCT meta-analysis, the WHO Brief Intervention and Contact (BIC), a program of 9 follow-up contacts significantly lowered the odds of suicide after an attempt by 80%, whereas cognitive-behavioral therapy (CBT) was not significantly protective [91].

A key target for contact enhancement strategies is patients discharged from the hospital following a suicide attempt, because they entail an exceptionally high risk of subsequent suicide attempt and completion [92], and they tend to experience barriers in their access to proper, outpatient mental healthcare, favoring loss of adherence during follow-up [93]. Motto and Bostrom pioneered this method by randomly assigning 843 patients who refused follow-up visits to either receiving a total of 24 letters over the following 5 years or a control group [94]. Two years after inclusion to the study, suicide was less than half likely among those who received the contact intervention, and up to 25% recipients answered back with thankful expressions. Accordingly, substantial attention has been put towards these low-resource, nonintrusive brief contact interventions (BCI). In general, BCI use letters [95], postcards [96], telephone calls [97], and/or a combination of all of them [98] for contact maintenance. One particular brief intervention, the widely implemented safety planning intervention (SPI), includes prioritizing coping strategies, addressing access to suicidal means, and enhancing outreach to professionals if suicidal urges emerge [99]. SPI was recently combined with a telephone call strategy and showed almost 50% fewer suicidal behaviors than treatment as usual in a series of Veteran Affairs hospitals [100].

Population-Level Suicide Prevention: Suicidal Individuals Versus Suicidal Populations

Since Durkheim's seminal book *Le Suicide* [101], it is accepted that suicide rates are determined, at least partially, by causal factors that act at an ecological level, "whose action is felt by society as a whole." Using Rose's words, "why some individuals have high blood pressure is a different question than why some populations have more burden of high blood pressure?" [102]. The use of group-level factors to model individual-level outcomes has been common in epidemiology, including psychiatric epidemiology, over the twentieth century. In an early example, Faris and Dunham documented that rates of psychosis were higher in urban areas of Chicago compared with rural areas [103], leading to a century of hypotheses about environmental determinants of schizophrenia risk [104].

Causal factors that are shared by a whole social group, such as urban dwelling, have been coined "integral variables" [105], and their effect cannot, by definition, be measured comparing individuals who are within the same group. Instead, they require between-group comparisons using ecologic designs that focus on groups of individuals as legitimate units of analysis [106, 107]. Several examples illustrate how suicide can be conceptualized from an ecological perspective: some countries, such as Latvia, have 5 times higher incidence rates than others, like Greece (<https://data.oecd.org/healthstat/suicide-rates6>), which prompts questions about the economic and cultural conditions that may be invariant across country but that can be examined to understand risk. In the USA, suicide rates in rural areas double those of urban areas [108]. Even within a city, like London, areas with higher ecological indices of social deprivation entail higher suicide rates [109].

However, suicide prevention efforts have characteristically tried to model suicide risk [110] and predict suicide relying solely on individual-level correlates. As mentioned, several current research initiatives seek to improve suicide prediction through machine learning algorithms based on datasets that include information from individuals' medical records [58•], speech analysis [111], and real-world behaviors measured through cell phone geolocation [112].

In attempts to understand causation of suicide, researchers often choose a frame of reference that includes a finite set of potential causes [107] and depends mainly in their field of knowledge: for example, a psychiatrist and a sociologist will consider different potential causes. By discarding what is outside our frame of reference, we generate an asymmetry on the way we look at things that permits cause-effect directionality [112]. Hence, the frame of reference and the scope of interest of the researcher determine which potential causes are considered [107], and complex systems with dynamic interactions between ecological and individual factors and feedback loops are usually reduced to a simpler thought model. As a result, causal relations tend to be ascertained at a particular level of

organization, usually the individual one in the field of suicidology, determined by the system delimited by our focus (factors within the system can be identified and related), and findings' validity is often limited to such system.

However, "a system never exists in isolation" [107]. As a result, there is growing interest in the study of how macro-level characteristics affect outcomes independently of individual variables, as well as how both levels interact [113]. In psychiatry, the interaction of the molecular, the individual, and the social levels in shaping mental suffering, disease, and illness was famously acknowledged by the late Engels's synthesis of the bio-psycho-social medical model [114]. Multilevel epidemiology has emerged as a response to this interest, as both a thinking framework and a set of tools that allow for the consideration of a hierarchy of multiple levels of causation for epidemiologic analyses. Tools and analyses to integrate and analyze a wide range of potential predictive factors through data science initiatives and machine learning are growing [115–117•], with potential to aid in prediction tools for suicide risk. These tools can be partnered with rich exploration of the social and political settings with which suicide risk also occurs in order to inform the broader environmental factors that predict risk.

There are three broad categories of interventions aimed at lowering the risk of suicide at the population level: universal and specific education campaigns, regulations in mass media coverage, and restriction of access to means.

Two evidence-based educational strategies stand out: the implementation of school-based suicide prevention and intervention programs [118, 119] and the identification and training of the so-called "emergent gatekeepers" [120], people who may have contact with those with suicidal thoughts without having been trained and designated as professionals (teachers, police, etc.).

The well-established influence of media reporting of suicide stories on subsequent suicide rates [121–123], usually referred to as the "Werther effect" and framed within the broader behavioral contagion theory [124], has provided an opportunity for intervention through a variety of reporting recommendation guidelines [125]. In general, these guidelines seek to foster responsible, non-sensationalist coverage of suicide and related events.

Theoretically, media also plays a role in means restriction, because it can reduce the population's "cognitive-access" [126] to suicide by purposely avoiding the coverage of key news, like an emerging suicide method or the suicide of a celebrity [123, 127]. However, by restriction of the access to suicide means we usually refer to a series of evidence-based interventions to physically prevent the population from accessing potentially lethal means such as pesticides [128], medications [129], suicide hotspots [130•], or firearms. The means reduction approach builds on evidence suggesting that ease of access influences the risk of attempting suicide [131], especially in impulsive suicidal behaviors [132]—the most

frequent type as nearly half suicide attempt survivors report a suicidal process, the interval between the onset of a suicidal thought and subsequent suicide attempting, of 10 min or less [133]. Accessibility also impacts method choice: up to 85% self-poisoning patients report that easy availability obtained their choice of poison [134].

Method substitution is the flip side of this coin. Reducing the access to lethal means tends to be even more effective if the alternative method available for substitution has a lower associated lethality, due to a lower inherent deadliness or to a higher ability to abort mid-attempt. For example, firearms, which can be found in roughly 33% of homes and account for 51% of total suicides in the USA, have twice the associated lethality of gas poisoning and 50 times that of drug overdose [131]. Accordingly, several studies using a variety of epidemiological designs have concluded higher risks of suicide for people who live in a household with firearms [135], after controlling for potential confounders [136], as well as higher suicide rates in states where gun ownership levels are higher [137].

Conclusion

In summary, suicide remains a substantial global contributor to causes of death, especially among those at younger age, and is increasing at an unprecedented rate in the USA. Non-fatal self-injury is also increasing, and together, the trends in self-injurious behavior raise questions about the causes, interventions, and preventive measures that should be taken. Prevention and treatment are often pointed towards high-risk groups, such as those with repeated suicide attempts, who are at increased risk of dying by suicide, but may miss the majority of suicide decedents who do not come into contact with the mental health care system and act impulsively. Conceptualizing suicide and its causes as a multilevel process that unfolds across the life course, with causes at higher geographic levels as well as individual levels, may be useful to develop programs that can have the most impact on population health, and innovative prevention and intervention programs that engage new technologies are in development but require additional evidence. Suicides are preventable and tragically destabilizing for individuals who recover from attempts, and for families of those affected. In the next generation of suicide research, it is critical to examine factors beyond the proximal and clinical to allow for a reimagining of prevention that is life course and socially focused.

Compliance with Ethical Standards

Conflict of Interest Gonzalo Martínez-Alés reports a grant from La Caixa Foundation LCF/BQ/AA17/11610021. The other author declares that there are no conflicts of interest.

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LETTER



Invasive mechanical ventilation for people with severe mental disorders: recent trends in incidence and in-hospital mortality

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Dear Editor,

The shortened life expectancy of people living with severe mental disorders (SMD) [1] is partially determined by worse outcomes than the general population following admission to intensive care units (ICUs) [2]. To better understand health care delivery for SMD patients within ICUs, we examined recent trends in use and outcomes of mechanical ventilation (MV) for critical patients with and without SMD.

Using the nationally representative Spanish Health Ministry's National Hospital Database, we selected all records of adults aged 15–69 years featuring an MV procedure between January 1, 2000 and December 31, 2015. International Classification of Diseases 9th Edition Clinical Modification (ICD-9-CM) codes for continuous invasive MV were: 96.70 (unspecified duration), 96.71 (<96 consecutive hours), and 96.72 (≥96 consecutive hours). We excluded patients aged ≥70 years as people with SMD have 15 years shorter life expectancy [1] and Spain's current life expectancy is 83 years [3]. Study groups were: SMD (ICD-9-CM codes 295–298: schizophrenia, episodic affective disorder, delusional disorder or other non-organic psychotic disorder) and non-SMD. Incidence rates were calculated per 10,000 total discharges of patients aged 15–69 years. Long-term MV and in-hospital mortality were defined as the proportion of procedures lasting ≥96 consecutive hours and the case fatality rate (CFR), respectively, both per 100 MV cases. To study trends, we used joinpoint regressions. These generalized

linear models allow for the estimation of average annual percentage changes (AAPC) with 95% confidence intervals (95% CI) over a time period, assuming a Poisson distribution [4].

Of 338,189 records, 9195 (2.7%) included an SMD diagnosis. Between 2000 and 2015, the incidence of MV more than doubled among SMD patients, from 1.4 to 3.3 procedures per 10,000 discharges (AAPC 4.6%; 95% CI 3.3, 5.9), while it remained unchanged in the non-SMD group (0.04%; 95% CI –0.4, 0.5) (Fig. 1a). Use of prolonged MV, conversely, increased only among cases without SMD (1.2%; 95% CI 1.0, 1.5) (SMD group: 0.4%; 95% CI –0.5, 1.3) (Fig. 1b). Finally, CFR decreased in both SMD (–1.8%; 95% CI –2.9, –0.7) and non-SMD patients (–1.4%; 95% CI –1.7, –1.2) (Fig. 1c). Notably, SMD patients were a median 5 years younger and included higher proportions of patients with no detected comorbidity according to the Charlson index (59.0% vs. 44.6%, $p < 0.001$) and of admissions due to poisoning than the non-SMD group (63.3% vs. 13.6%, $p < 0.001$), three characteristics that may help explain their lower overall mortality rate.

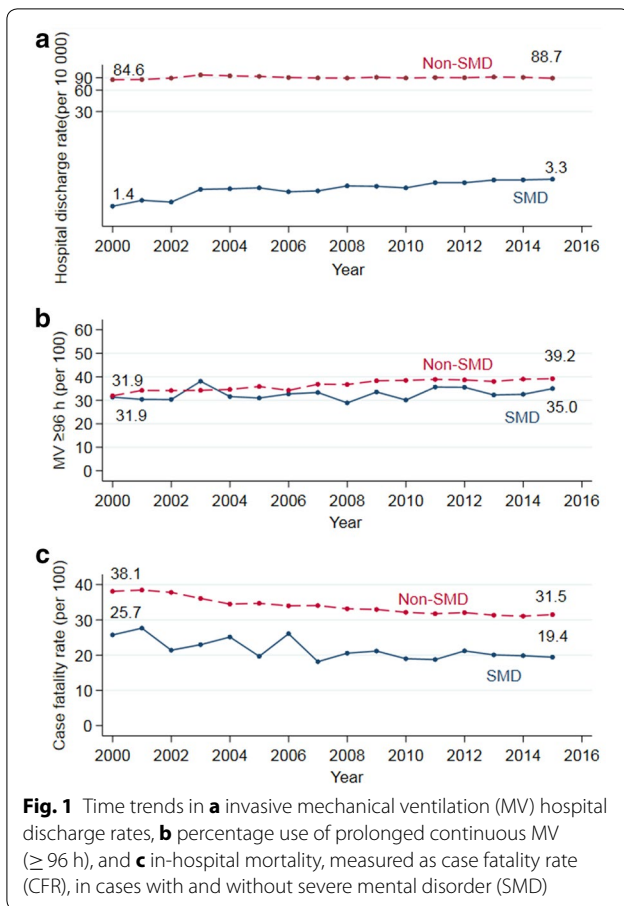
Our study is limited by potential coding inaccuracies. However, the quality of the data is audited regularly and errors, if present, would not affect differentially the two study groups. Also, although we used 13 diagnostic fields to detect SMD, some diagnoses may have been missed, potentially reducing between-group differences [5].

In conclusion, between 2000 and 2015, MV use increased only among SMD patients, and comparable decreasing trends in mortality were observed both in people with and without SMD. Future research should explore reasons for the observed increase of MV use in

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the SMD group and examine these patients' long-term prognosis following hospital discharge.

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Author contributions

Funding acquisition: CB. Study conception and design: GMA, TLC, CB. Data collection and analysis: GMA, TLC, CB. First draft: GMA, TLC, CB. All authors

commented on previous versions of the manuscript, and read and approved the final manuscript.

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Data availability

The data come from anonymized registries. Because of the confidentiality agreement signed with the Ministry of Health, Consumer Affairs and Social Welfare, the data from this study cannot be shared with third parties. The authors did not have special access privileges. Should any researcher wish to gain access to these data, they can do so by applying directly to the Ministry through the following link: <https://www.msbs.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/SolicitudCMBD.htm>.

Compliance with ethical standards

Conflicts of interest

The authors declare no conflict of interest in relation to this manuscript.

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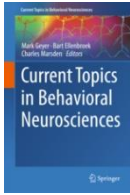
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Current Topics in Behavioral Neurosciences (CTBN)

Mark A. Geyer, Charles A. Marsden, Bart A. Ellenbroek, Thomas R.E. Barnes, Susan L. Andersen (Eds.)

To whom it may concern,

This is to certify that the work entitled “*Why are suicide rates increasing in the United States? Towards a multi-level reimagination of suicide prevention*”, authored by Gonzalo Martínez-Alés, Daniel Hernández-Calle, Nicole Khauli, and Katherine M. Keyes, is accepted for publication in a forthcoming volume devoted to the *Behavioral Neurobiology of Suicide and Self Harm* for the *Current Topics in Behavioral Neurosciences* series, published by Springer.

Kind regards

Enrique Baca-García

Editor, *Behavioral Neurobiology of Suicide and Self* volume

RESEARCH

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Effect of dementia on the incidence, short-term outcomes, and resource utilization of invasive mechanical ventilation in the elderly: a nationwide population-based study

Carmen Bouza^{1*} , Gonzalo Martínez-Alés^{2,3} and Teresa López-Cuadrado⁴

Abstract

Background: Though the prevalence of dementia among hospitalized patients is increasing, there is limited population data in Europe about the use of life-support measures such as invasive mechanical ventilation in these patients. Our objective is to assess whether dementia influences the incidence, outcomes, and hospital resource use in elderly patients undergoing mechanical ventilation.

Methods: Using ICD-9-CM codes, all hospitalizations involving invasive mechanical ventilation in adults aged ≥ 65 years were identified in the Spanish national hospital discharge database covering the period 2000–2013. The cases identified were stratified into two cohorts (patients with or without dementia) in which main outcome measures were compared. The impact of dementia on in-hospital mortality and hospital resource use were assessed through multivariable models. Trends were assessed through joinpoint regression analysis and results expressed as average annual percentage change.

Results: Of the 259,623 cases identified, 5770 (2.2%) had been assigned codes for dementia. Cases with dementia were older, had a lower Charlson comorbidity score, and less frequently received prolonged mechanical ventilation or were assigned a surgical DRG. Circulatory disease was the most common main diagnosis in both cohorts. No significant impact of dementia was observed on in-hospital mortality (adjusted OR 1.04, [95% CI] 0.98, 1.09). In the cohort with dementia, the incidence of mechanical ventilation underwent an average annual increase over time of 5.39% (95% CI 4.0, 6.7) while this rate was 1.62% (95% CI 0.9, 2.4) in cases without dementia. However, unlike this cohort, mortality in cases with dementia did not significantly decline over time. Geometric mean hospital cost and stay were lower among cases with than without dementia (-14% [95% CI -12% , -15%] and -12% [95% CI, -9% , -14%], respectively), and these differences increased over time.

Conclusion: This nationwide population-based study suggests no impact of dementia on in-hospital mortality in elderly patients undergoing invasive mechanical ventilation. However, dementia is significantly associated with shorter stay and hospital costs. Our data also identifies a recent marked increase in the use of this life-support measure in elderly patients with dementia and that this increase is much greater than that observed in elderly individuals without dementia.

Keywords: Dementia, Elderly, Mechanical ventilation, Incidence, Outcomes, Trends

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Background

Dementia is one of the greatest health problems among persons aged 65 years or older worldwide. Because of population aging and a lack of effective prevention and treatment measures, it has been estimated that in the foreseeable future, the number of affected persons will double [1, 2].

The prevalence of dementia among hospitalized patients is also increasing [3–5], but the balance of potential benefits and harm of intensive care interventions in this population is unclear. In fact, the last few years have witnessed intense debate regarding life-support intensive treatment in patients with dementia such as invasive mechanical ventilation (MV) [6–9]. MV is a key component of the management of critically ill patients with acute or chronic respiratory failure. However, it is associated with a high mortality [10], with short- and long-term complications [11, 12], and requires a complex care level with a substantial impact on hospital resources [13].

Despite these considerations, few studies have examined trends in its use in patients with dementia. The scarce data available come from the USA and Canada where several authors have reported a sustained increased use of MV in patients with dementia in the past few decades [14, 15] with clinical outcomes comparable to those observed in patients without dementia [16].

Spain is a rapidly aging country and dementia prevalences are among the highest in the world (<https://www.alzheimer-europe.org/Policy-in-Practice2/Country-comparisons/2013-The-prevalence-of-dementia-in-Europe/Spain>). This determines the need to characterize the use of MV and its trends in these patients since the use of effective and safe therapeutic technologies and the appropriate use of healthcare resources are priority objectives in a quality health system. Accordingly, this study sought to examine the characteristics of MV and its recent trends in incidence, associated mortality, and hospital resource use in patients ≥ 65 years with and without dementia based on data from Spain's national hospital discharge database.

Methods

Study design and data sources

We performed a retrospective population-based study using the Spanish Health Ministry's National Minimum Basic Data Set (MBDS). This official database gathers information derived from discharge reports from all acute-care hospitals in Spain. For each hospitalization, demographic and clinical information is provided including a main diagnosis, 13 secondary diagnoses, and up to 20 procedures coded at each center before patient discharge according to International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes as well as corresponding diagnosis-related group

(DRG) codes. This information, whose registration is mandatory by law in the National Health System, is considered to be representative of the national population as the database covers over 90% of all annual hospital admissions produced in our country [17].

To calculate incidence rates, we used population data provided by the Spanish Statistics Institute [18]. Hospital admissions data were provided by the Ministry of Health, Resources and Welfare [17]. All data used are anonymous so, according to Spanish law, the need was waived for informed consent [19].

Study population: case definitions and identification

Hospitalizations involving subjects ≥ 65 years who received MV from January 1, 2000, to December 31, 2013, were identified using the ICD-9-CM codes: 96.70 (continuous invasive MV of unspecified duration), 96.71 (continuous invasive MV < 96 consecutive hours) and 96.72 (continuous invasive MV ≥ 96 consecutive hours). These codes are considered specific, stable, and valid [20].

According to ICD-9-CM coding norms, one of these codes is assigned to hospitalized patients who require MV except if used during a routine surgical procedure. Postsurgery MV is coded if lasting more than 2 days or if the clinician reports its duration was longer than planned. MV duration was measured from the moment of endotracheal intubation [17].

Dementia is a clinical syndrome characterized by a global, progressive cognitive impairment that generates functional decline and disability [21]. A variety of brain-damaging conditions, such as degenerative, vascular, metabolic, or toxic brain disease, can lead to dementia, and although the most frequent cause of dementia from middle age to elderly is Alzheimer's disease, most patients suffer from a mixture of different pathologies [21]. We defined dementia as the presence in any of the diagnoses entered in the database of the ICD-9-CM codes: 290.0–290.9 (dementias), 291.1 (alcohol-induced persisting amnesic disorder), 291.2 (alcohol-induced persisting dementia), 292.82 (drug-induced persisting dementia), 292.83 (drug-induced persisting amnesic disorder), 294.0 (amnesic disorder in conditions classified elsewhere), 294.1 (dementia in conditions classified elsewhere), 294.2 (dementia, unspecified), 294.8 (other persistent mental disorders due to conditions classified elsewhere), 294.9 (unspecified persistent mental disorders due to conditions classified elsewhere), 331.0 (Alzheimer's disease), 331.1 (frontotemporal dementia), 331.2 (senile degeneration of the brain), 331.7 (cerebral degeneration in diseases classified elsewhere), 331.82 (dementia with Lewy bodies), and 331.9 (cerebral degeneration, unspecified). Similar broad definitions of dementia have been used by others [14] to improve case detection.

To assess the comorbidity burden, we used the Charlson index score validated by Deyo [22] and improved for ICD-9-CM [23] according to secondary diagnoses. For the purposes of this study, dementia itself was excluded in the Charlson Index [24].

For every case, the main diagnostic group was assessed according to the ICD-9-CM chapters: infectious disease (001–139), neoplasms (140–239), endocrine diseases (240–279), hematological diseases (280–289), neurological diseases (320–389), diseases of the circulatory system (390–459), respiratory diseases (460–519), diseases of the digestive system (520–579), diseases of the genitourinary tract (580–629), diseases of the skin and subcutaneous tissue (680–709), diseases of the musculoskeletal system and connective tissue (713–739), and injury-poisoning (800–999).

Data analysis

We conducted a descriptive and comparative analysis of cases with and without dementia, including demographic and clinical information, comorbidity burden, and hospital mortality, stay, and costs. Charlson comorbidity scores are provided as a continuous variable and as categorical with 4 groups (0, 1–2, 3–4, >4) of increasing severity and impact on outcomes [25]. Categorical variables are expressed as absolute frequencies and percentages while continuous variables are given as geometric means and geometric standard deviation (SD), as geometric means are less influenced by extreme values than arithmetic ones. To test differences in categorical variables, we used Pearson's chi-square test.

In-hospital mortality was estimated as the number of deaths relative to the number of cases and expressed as a percentage, or case fatality rate (CFR). To examine the effect of dementia on mortality, stay, and costs, we conducted regression models (logistic regressions for mortality and linear regressions of log-transformed stay and costs) and adjusted them in two multivariable models. Model 1 was adjusted for baseline characteristics (age, sex, Charlson index) whereas model 2 also included the principal diagnosis at admission and MV duration. Results are expressed as odds ratios (OR) with 95% confidence intervals (for mortality) and geometric means ratio with 95% confidence intervals (for stays and costs).

We examined temporal trends in MV incidence rate (per 100,000 people and per 10,000 hospital discharges), proportion of MV cases with dementia, prolonged MV (defined as a duration of ≥ 96 consecutive hours according to the ICD-9-CM codification system), and CFR. To this end, we used joinpoint regression models—generalized linear models that assume a Poisson distribution [26]. In these models, any apparent trend can be statistically assessed through a Monte Carlo permutation method

[27]. Trends are presented as the average annual percentage change (AAPC), a summary measure of the overall trend over the study period. To compare the AAPC of both study groups, we examined whether their regression mean functions were parallel, allowing for different intercepts, using the Pairwise comparison parallel test. In addition, we analyzed trends in length of stay and costs using Cuzick's *p*-trend test.

All tests were performed using the packages STATA 15 (StataCorp. LP, College Station, TX, USA) and Joinpoint Regression 4.7.0.0. Significance was set at $p < 0.05$.

Results

Out of the 19,979,322 hospitalizations in persons aged ≥ 65 years produced over the 14-year study period, 259,623 cases underwent MV. Of these, 5770 (2.2%) were cases with dementia.

As may be seen in Table 1, in the dementia cohort, the proportions of women and older age strata were higher than in the cohort without dementia. The Charlson score, however, was lower indicating a lower comorbidity burden among those with dementia. Among the main comorbidities, we should highlight a greater presence of cerebrovascular disease in the group of patients with dementia. Circulatory disease was the most common main diagnosis in both cohorts and was followed with disparate frequency in each one by respiratory disease, injury-poisoning, and digestive disorders. Conversely, cancer was much less frequent in the cases with dementia. Registries including dementia corresponded more to smaller hospitals, and patients less frequently received prolonged MV or were assigned a surgical DRG than in the non-dementia group. The cohort with dementia showed a slightly, yet significantly, higher in-hospital mortality, and this difference was attributable only to cases subjected to short-duration MV (Additional file 1: Table S1). However, as may be observed in Table 2, according to the logistic regression analysis adjusted for age, sex, comorbidity burden, main diagnosis, and MV duration, dementia had no significant impact on in-hospital mortality.

Among the survivors, 78% of cases with dementia and 81% of those without dementia were discharged home while 16.3% and 15.1% respectively were discharged to long-term care centers.

Both geometric mean stay and hospital costs for the dementia group were significantly lower than for the non-dementia group (Table 2). Further, multivariate analysis of the impacts of dementia on hospital resource use indicated that dementia was associated significantly with a shorter adjusted mean hospital stay and lower mean hospital costs per case.

Table 1 General characteristics of adults ≥ 65 years receiving invasive mechanical ventilation

	With dementia 5770 (2.2)	Without dementia 253,853 (97.8)	OR (95%CI)	<i>p</i> value
Gender women	2702 (46.8)	96,946 (38.2)	1.43 (1.35, 1.50)	< 0.001
Age				
65–74 years	1787 (31.0)	131,717 (51.9)	Ref.	
75–84 years	3166 (54.9)	108,990 (42.9)	2.14 (2.02, 2.27)	< 0.001
> 84 years	817 (14.1)	13,146 (5.2)	4.58 (4.21, 4.99)	< 0.001
Charlson Index score				
0 points	1891 (32.8)	77,478 (30.5)	Ref.	
1–2 points	2932 (50.8)	124,467 (49.0)	0.97 (.91, 1.02)	0.235
3–4 points	734 (12.7)	37,678 (14.8)	0.80 (0.73, 0.87)	< 0.001
> 4 points	213 (3.7)	14,230 (5.6)	0.61 (0.53, 0.71)	< 0.001
Main Charlson comorbidities				
Diabetes	1476 (25.6)	59,879 (23.6)	1.10 (1.03, 1.14)	< 0.001
Cerebrovascular disease	1048 (18.2)	18,972 (7.5)	2.75 (2.57, 2.94)	< 0.001
COPD	1005 (17.4)	54,918 (21.6)	0.76 (0.71, 0.82)	< 0.001
Heart failure	836 (14.5)	47,921 (18.9)	0.73 (0.68, 0.78)	< 0.001
ICD-9-CM main diagnosis				
Circulatory	1751 (30.3)	98,683 (38.9)	0.69 (0.65, 0.73)	< 0.001
Respiratory	984 (17.0)	39,379 (15.5)	1.12 (1.04, 1.20)	0.001
Injury-poisoning	910 (15.8)	27,338 (10.8)	1.55 (1.44, 1.67)	< 0.001
Digestive	805 (14.0)	29,621 (11.7)	1.23 (1.14, 1.32)	< 0.001
Cancer	364 (6.3)	29,229 (11.5)	0.52 (0.47, 0.58)	< 0.001
No. of hospital beds				
< 200	691 (12.0)	26,929 (10.6)	Ref	
200–500	1927 (33.4)	71,698 (28.2)	1.05 (0.96, 1.14)	0.302
501–1000	1774 (30.8)	87,898 (34.6)	0.79 (0.72, 0.86)	< 0.001
> 1000	1378 (23.9)	67,327 (26.5)	0.80 (0.73, 0.87)	< 0.001
DRG surgical	2455 (42.6)	145,001 (57.2)	0.56 (0.53, 0.59)	< 0.001
Mechanical ventilation ≥ 96 h	1729 (30.0)	85,162 (33.6)	0.85 (0.80, 0.90)	< 0.001
In-hospital mortality (CFR)	2992 (51.9)	123,445 (48.6)	1.14 (1.08, 1.20)	< 0.001

Data presented as number of cases (%)

OR odds ratio, CI confidence interval, COPD chronic obstructive pulmonary disease, DRG diagnosis-related group, CFR case fatality rate

Table 2 Impact of dementia on in-hospital mortality and hospital resource use

	With dementia (%)	Without dementia (%)	Crude OR (95% CI)	Model 1 Adjusted OR (95% CI)	Model 2 Adjusted OR (95% CI)
CFR	51.9	48.6	1.14 (1.08, 1.20)	1.05 (0.99, 1.1)	1.04 (0.98, 1.09)
	Geometric mean (SD)	Geometric mean (SD)	Ratio of geometric means (95% CI)	Adjusted ratio of geometric means (95% CI)	
Hospital stay, days	11.16 (3.20)	14.01 (3.19)	0.80 (0.77, 0.82)	0.85 (0.82, 0.87)	0.88 (0.86, 0.91)
Costs, €	10,423 (2.34)	12,855 (2.40)	0.81 (0.79, 0.83)	0.83 (0.81, 0.85)	0.86 (0.85, 0.88)

Model 1: adjusted for sex, age, Charlson index

Model 2: adjusted for sex, age, Charlson index, main diagnosis, and length of MV

CFR case fatality rate, SD standard deviation

Temporal trends

Rates of MV use referred to hospital discharges and the general population underwent a significantly greater increase among the subjects with dementia compared to those without (Table 3). In patients with dementia, the rate of MV use per 10,000 hospital discharges went up from 1.76 in 2000 to 3.57 in 2013, with an AAPC of 4.7%. Meanwhile, in patients without dementia, the rate of MV use per 10,000 hospital discharges went up from 114.5 in 2000 to 131.3 in 2013 with an AAPC of 0.91%. According to the comparability test, trends of MV in dementia and non-dementia cases were different (p value for test for parallelism = 0.005). The population incidence of MV in people with dementia rose from 3.1 to 6.9 per 100,000 inhabitants ≥ 65 years, yielding an AAPC of 5.39%, while in the non-dementia group it increased from 203.6 to 253.3, for an AAPC of 1.62% (Fig. 1). According to the comparability test, population incidence trends in dementia and non-dementia were also different (p value for test for parallelism = 0.03).

Table 3 also provides temporal trends in the use of VM ≥ 96 h and in-hospital mortality (CFR), indicating that subjects with dementia underwent no significant changes over the study period, while in the non-dementia cohort the use of prolonged MV increased and mortality decreased. As shown in Fig. 2, cases with dementia have not followed the descending trend shown by the cases without dementia; rather, mortality has fluctuated over time.

Figure 3 illustrates that geometric mean hospital stay in the cohort with dementia has steadily declined over time, while it has been relatively stable in the cohort without dementia. Geometric mean hospital costs per case have risen markedly over the study period. This increase has been nevertheless lower among cases with dementia, and inter-cohort differences have persisted (Fig. 3).

Discussion

The findings of this population-based study indicate that the use of MV in elderly persons diagnosed with dementia has shown a marked increase in Spain between the

years 2000 and 2013. Further, this increase has been higher than that observed in their dementia-free counterparts. They also reveal that while no impacts of dementia on hospital mortality were detected, the declining trend in mortality produced in patients without dementia was not observed. In addition, compared with subjects free of dementia, these individuals incur lower hospital costs and length of stay.

As far as we know, this is the first study to characterize the pattern of MV use in adults ≥ 65 years with and without dementia in a European country. The demographic and clinical characteristics of our cases are similar to those described in the USA and Canada [14, 15], although dementia appears as notably less frequent among those receiving MV in our setting. Only 2.2% of hospitalized adults aged ≥ 65 years undergoing MV had been assigned a code for dementia, contrasting with the 15% and the 8.6% rates described in those studies. Our results show in the cohort of patients with dementia a marked increase in the incidence of MV with an average annual increase of 5.39%, which is much higher than the 1.62% observed in the cohort without dementia. Notwithstanding, the increase detected was markedly lower than that reported by Lagu (11.4%) and by Borjaille (7.8%) in adults ≥ 65 years with dementia [14, 15]. In part, these differences could be explained by the very different healthcare systems and the organizational models used for the care of critically ill patients between countries [28]. We should not forget that in a healthcare setting, offer is an important regulator of demand. Effectively in the USA, the increased use of MV in patients with advanced dementia has been linked to a greater availability of beds in intensive care units [29]. In Spain, with its universal, equal-access healthcare system, it is estimated that in 2010 there were some 9.6 ICU beds per 100,000 inhabitants [30, 31] while in the USA this was around four times this figure in 2009 [32]. But, in spite of these differences, our data are in line with those reported in North America and contrast with prior studies indicating that acute care patients with dementia are treated substantially less aggressively than patients without dementia [8].

Table 3 Trend analysis

	MV in cases with dementia			MV in cases without dementia			Parallelism test
	2000	2013	AAPC (95% CI)	2000	2013	AAPC (95% CI)	
Proportion (%)	1.51	2.64	3.8 (3.0, 4.5) [†]	98.5	97.4	-0.1 (-0.1, -0.1) [†]	$P < 0.001$
Hospital discharge rate (per 10,000)	1.76	3.57	4.71 (3.6, 5.8) [†]	114	131	0.91 (0.4, 1.4) [†]	$P = 0.005$
Population rate (per 100,000)	3.1	6.9	5.39 (4.0, 6.7) [†]	203.6	253.3	1.62 (0.9, 2.4) [†]	$P = 0.030$
MV ≥ 96 h (%)	24.6	28.4	-0.8 (-2.3, 0.7)	31.2	34.9	0.99 (0.7, 1.3) [†]	$P = 0.031$
CFR (%)	55.9	50.2	-0.30 (-1.1, 0.5)	51.9	44.5	-1.19 (-1.3, -1.0) [†]	$P = 0.10$

MV invasive mechanical ventilation, AAPC average annual percentage change, 95%CI 95% confidence interval, CFR: case fatality rate

[†]Statistically significant

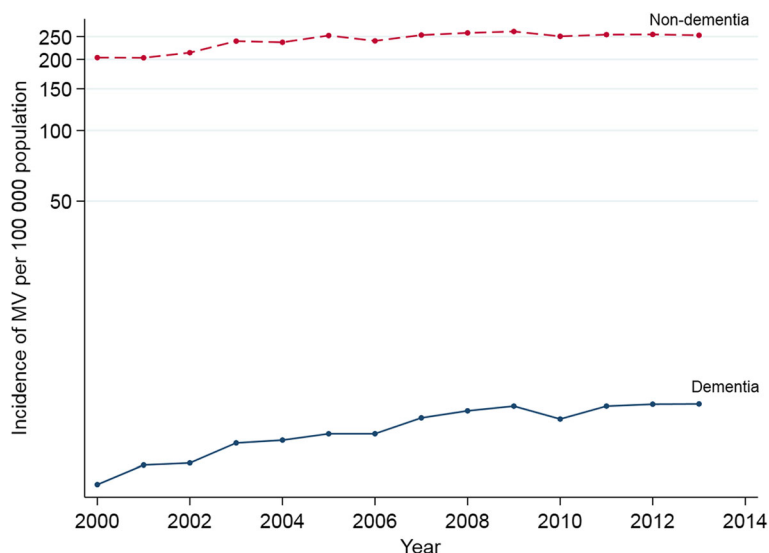


Fig. 1 Trends in invasive mechanical ventilation incidence rates in patients with and without dementia. The figure shows the changes observed over time in incidence rates. The cohort with dementia reaches a greater increase than the cohort without dementia

Our dementia group showed an older age and higher percentage of women, as described by others [16]. However, our cases had a lower comorbidity burden which could be partly due to the different score system used as there is still no standardized method to assess this issue despite its important role in patient’s outcomes [33]. For this study, we selected the Charlson comorbidity index as it has shown a similar capacity to scales based on physiological scores to predict mortality in critically ill patients [34].

As expected, in-hospital mortality was really high in both cohorts. But, a main finding of our study was the lack of significant differences in CFR between both cohorts once adjusted for remaining clinical-demographic variables, meaning that dementia has not had a significant impact on hospital mortality in individuals ≥ 65 years subjected to MV. This finding, which is in line with the data reported by Lagu et al. [16], also suggests the use of MV in persons with dementia in our country complies (at least in terms of mortality as an effect

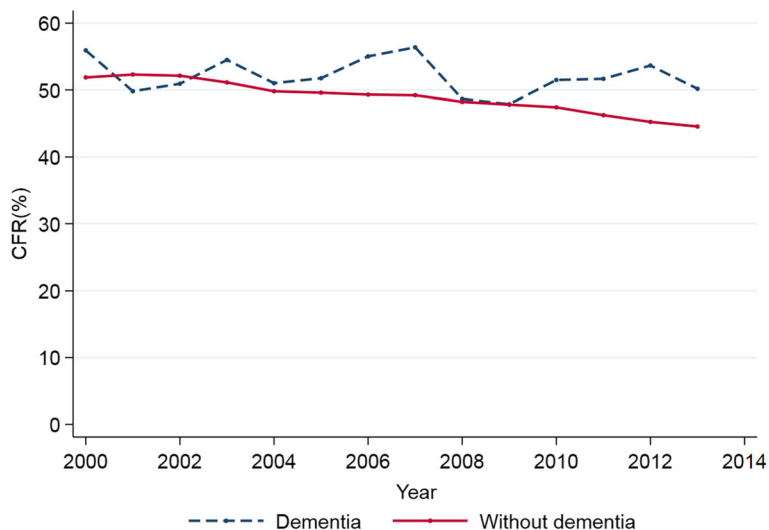
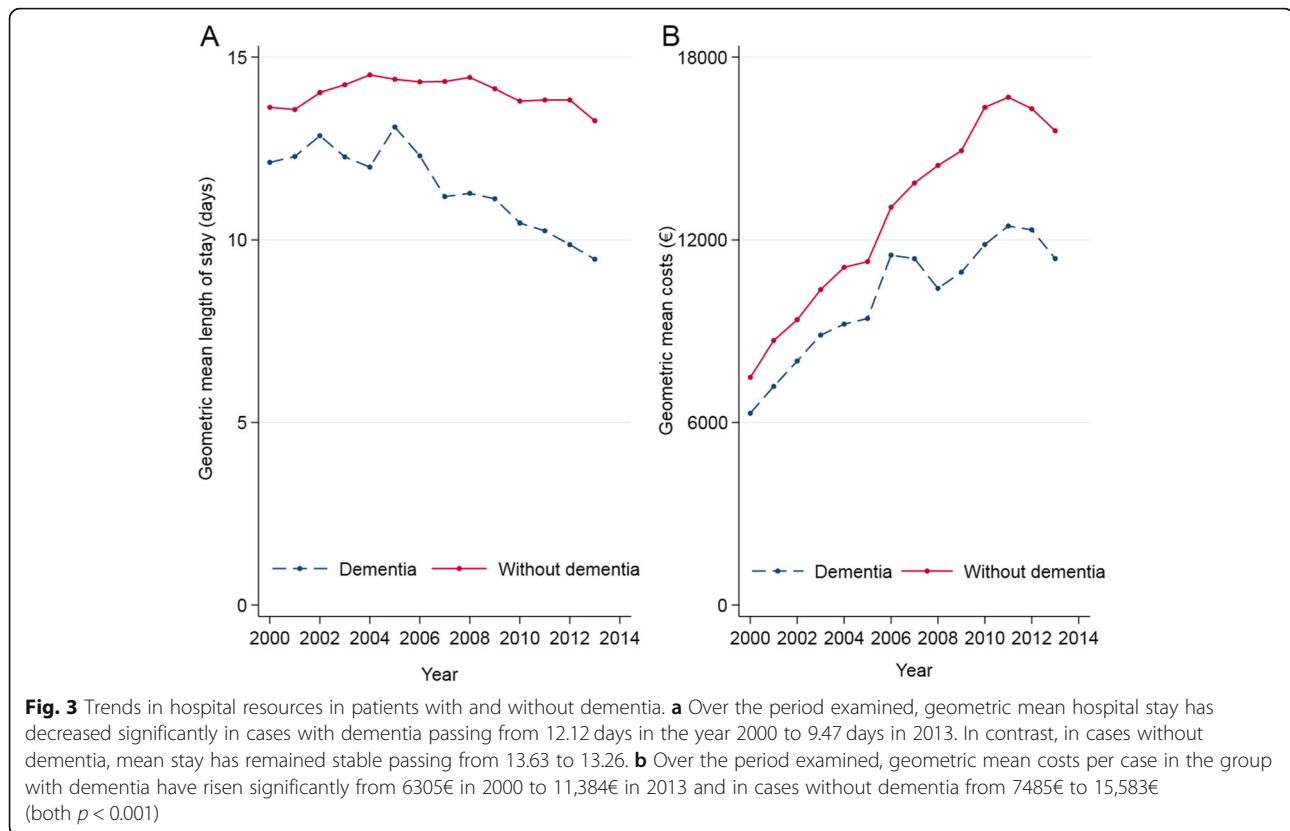


Fig. 2 Trends in in-hospital mortality in MV episodes of patients with and without dementia. The figure shows the changes observed over time in in-hospital mortality. Note that cases with dementia do not show the downward trend detected in the cases without dementia; rather, they feature a fluctuating trend over the period of study



measure) with the quality standard of its use in patients ≥ 65 years without dementia.

Our trends analysis, nevertheless, indicates that while hospital mortality in the dementia-free cohort has steadily declined over the 14 years examined, which is consistent with literature reports [35], we observed no parallel changes in the dementia cohort.

Something similar can be said about the trend observed in the use of hospital resources. While some studies have shown that dementia leads to longer mean hospital stay and costs in older patients admitted because of acute illness [3, 4], our finding is consistent with more recent descriptions [16, 36] that these variables are significantly lower in patients with dementia. Our study also reveals that this reduced resource use in patients with dementia persists when the extent of MV was introduced as a covariate in the adjusted multivariate model. Additionally, trend analysis indicate that mean length of stay difference has increased over the years since while the mean hospital stay in cases without dementia has remained stable, it has progressively decreased in cases with dementia.

Unfortunately, the database design prevents any causal inferences or assessment of other reasons that could justify these trends, such as the existence of advanced directives, family preferences, or clinical practices toward the limitation of therapeutic efforts and the use, instead,

of comfort measures. We consider those data are fundamental and that it is necessary to study them in a prospective way.

Our observations extend the scarce available information on the incidence and short-term outcomes of the use of invasive technologies such as MV in adults aged ≥ 65 years with dementia, and perhaps, they can be of help in the existing debate about the use of these therapeutic measures in patients with dementia. Further, given the national population-based nature of our data, we feel they may be generalizable and of interest for clinical decision making and healthcare resource planning in an increasingly aging society for which a greater prevalence of dementia is foreseen in the near future [15, 37, 38].

Limitations

Our study has several limitations we should mention. When working with clinical-administrative data, sensitivity to detect the variables of interest depends directly on the discharge report completed by the responsible physician. There is evidence to suggest that dementia has been undercoded in discharge reports, especially in mild or complex cases [39]. To minimize this limitation, we used a broad definition of dementia in line with previous, similar studies [14, 16], even though these definitions have not been validated against clinical charts.

Moreover, MV is a major procedure which is easily identified in a patient's clinical record and whose ICD-9-CM codes are stable and validated [20]. However, we did not have access to staging information of our dementia cases. Given that an inverse relationship has been established between dementia severity and the frequency at which patients are hospitalized and that some clinical guidelines emphasize the need to treat persons with dementia at their homes [37], it is likely that our dementia cohort will contain a high proportion of mild-moderate severity cases. Our data source also prevents us from knowing other individual factors such as pharmacological treatments; the existence of an advance directive or their socio-cultural or educational level which makes it impossible to further characterize this cohort and stratify the results according to these factors. Nonetheless, given the universal character of our national health system with equal access to the whole population, aspects such as the socioeconomic level have not influenced the results obtained. Likewise, given the regulation of our national health system, we can assume that clinical and coding practices have not been related to economic incentives. Also, our database does not include physiology-based scores of common use in ICUs, such as APACHE or SAPS. Notwithstanding, Christensen and colleagues have shown that the Charlson comorbidity index performs similarly to physiology-based scores at predicting short- and long-term mortality for ICU patients [34]. Finally, because of this study's retrospective nature, we cannot rule out that temporal trends may, at least in part, be associated with different treatment practices during the long period of study. However, the population nature of our study, its main strength, means we can assume a lack of selection bias and can also extrapolate its results. In addition, RECORD recommendations for reporting of results were followed [40].

Conclusions

This nationwide population-based study reveals no impact of dementia on in-hospital mortality in elderly patients undergoing invasive mechanical ventilation. However, dementia is significantly associated with shorter stay and hospital costs. Our data also identifies a recent marked increase in the use of this life-support measure in elderly patients with dementia and that this increase is much greater than that observed in elderly individuals without dementia. This data have important implications for clinical decision-making and healthcare resource planning in an increasingly aging society for which a greater prevalence of dementia is foreseen in the near future.

Additional file

Additional file 1: Table S1. General characteristics and outcomes of cases by duration of invasive mechanical ventilation (MV). (DOCX 16 kb)

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Authors' contributions

All authors meet the International Committee of Medical Editors criteria for authorship. CB designed the study; participated in the acquisition, analysis, and interpretation of the data; drafted and revised the manuscript; and obtained funding. GMA participated in the statistical analysis, made substantial contributions to the interpretation of the data, and drafted and revised the manuscript. TLC participated in the acquisition and data curation, performed the statistical analysis and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data are anonymized and, according to Spanish law, are exempt from the necessity for informed consent. They come from hospital discharge records collected and de-identified by the Spanish Ministry of Health, Social Services and Equality. The authors requested and obtained access to the data from the Ministry and, due to a signed confidential agreement, cannot share these data with third parties. However, these records are publicly available for research purposes. Requests of access to the data should be addressed directly to the Ministry.

Ethics approval and consent to participate

Not applicable

Consent for publication

All authors have reviewed the manuscript and approved the publication.

Competing interests

The authors declare that they have no competing interests.

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