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Causes of mortality among adults with Down syndrome before and after the COVID-19 pandemic in Spain

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Abstract

Background The life expectancy of people with Down syndrome (DS) is limited by Alzheimer's disease (AD)-related deaths, mainly due to respiratory infections. The emergence of the COVID-19 pandemic could have changed known, past trends in mortality in this population. We analysed the differences in causes of mortality between individuals with DS deceased before and after the onset of the pandemic.
Method This is a cross-sectional study of adults with DS recruited at a tertiary, university outpatient clinic in Madrid, Spain. Demographic and clinical data were retrospectively collected from their medical records, including information on their deaths, if any.
Results Five hundred seventy-two adults were included in the study, and 67 (11.7%) died. The main cause of death was respiratory infections, which occurred in 36 participants [9 (45.0%) before, and 27 (58.7%) after the appearance of COVID-19]. No significant differences were found in the determinants of pre-pandemic and post-pandemic death after adjusting for age and AD, except for an association between the use of psychotropic medication and death in the post-pandemic period (odds ratio: 2.24; 95% confidence interval: 1.04–4.82). Vaccination against COVID-19 showed a marked protective effect against mortality (odds ratio: 0.0002; 95% confidence interval: $6.7e10^{-6}$ to 0.004).
Conclusions The appearance of COVID-19 has not impacted the overall trend of increase in mean age of death of adults with DS in our milieu, probably thanks to the very important protective effect of vaccination, which supports prioritising people with DS in future immunisation campaigns. The association between psychotropic medication use and mortality requires further exploration.

Keywords Alzheimer's disease, COVID-19, Down syndrome, mortality, respiratory infections

Introduction

The increased survival of people with Down syndrome (DS) in recent decades has modified the profile of co-morbidities and complications that were classically observed in this population. As their life expectancy currently exceeds 60 years (Benejam *et al.* 2020), it is quite common to find adults with chronic pathologies, among which Alzheimer's

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disease (AD) stands out. The tight relationship between AD and DS is due to the extra copy of the amyloid precursor protein gene, located on chromosome 21 (Wiseman *et al.* 2015; Ballard *et al.* 2016; Antonarakis *et al.* 2020), which leads to the accumulation of an excessive amount of β-amyloid peptides. The formation of amyloid plaques, which has been demonstrated even before the age of 40, is both sufficient and necessary to develop AD (Fortea *et al.* 2020).

Due to its progressive and irreversible course, AD has an enormous impact on the quality of life and on the mortality of adults with DS (Hithersay *et al.* 2019; Iulita *et al.* 2022). Respiratory infections constitute the main cause of hospitalisation and death, both for patients with sporadic AD in the general population and those with genetic forms of the disease, such as people with DS (Graversen *et al.* 2021). The prevalence of these infections is closely related to the progression of dementia and the development of neurogenic dysphagia, which facilitates aspiration pneumonia. In addition, people with DS show chronic immune dysregulation (Espinosa 2020; Illouz *et al.* 2021), making them more prone to respiratory infections even from infancy. Furthermore, as people with DS grow older, they are more likely to develop other co-morbidities such as obesity, diabetes, epilepsy and so on. These conditions can be associated with reduced lung capacity and altered immune responses, collectively contributing to an increased risk of pneumonias and making them a leading cause of death in this population (Santoro *et al.* 2021).

However, the emergence of COVID-19 in 2020 might have changed this picture (Real de Asua *et al.* 2021). In the general population, this infection has been shown to impact the mortality rate in younger age groups, with a log-linear increase with age among individuals older than 30 years (O'Driscoll *et al.* 2021). People with DS are especially vulnerable to COVID-19, with a four-fold greater likelihood than the general population of being hospitalised for this reason and a three-fold to ten-fold increased risk of mortality in the first 6 months of the pandemic (Hüls *et al.* 2021). In addition, during the first waves of the pandemic, adults with DS and dementia had a COVID-related mortality rate three times higher than that of non-COVID pneumonias (Real de Asua *et al.* 2021). Even after the beginning of vaccination campaigns, a study conducted in Madrid, Spain, reported that people with DS had a mortality rate 12.7 times higher than the general population (Esparcia-Pinedo *et al.* 2023).

In short, the onset of the pandemic and its related factors could have modified the profile and causes of mortality of individuals with DS. Exposed to a higher risk of COVID-19, these individuals could die at an earlier age, even without having developed the co-morbidities observed in the pre-pandemic period. The aim of the present study is to describe the causes of mortality in a cohort of adults with DS with and without dementia, before and after the onset of COVID-19. We have also compared these groups to determine whether the clinical profile of the individuals who died before and after the onset of the pandemic significantly differed.

Materials and methods

Study design and selection criteria

The present cross-sectional study includes a cohort of people with DS, whose data were readily available as they were already enrolled in a larger genetic sequencing study to identify single nucleotide polymorphisms associated with different dementia-related phenotypic variables. Samples and data from patients included in this study were provided by the Biobank Biobanco Hospital Universitario de La Princesa (ISCIII B.0000763), and they were processed following standard operating procedures with the appropriate approval of the Ethics and Scientific Committees. The cohort has been described fully elsewhere (Moreno-Grau *et al.* 2019). Individuals were selected among those who attended the Adult Down Syndrome Clinic of the Department of Internal Medicine at the Hospital Universitario de la Princesa, a tertiary care, university hospital in Madrid, Spain. All participants were adults over 16 years of age with a confirmed diagnosis of DS, either with a compatible karyotype or typical phenotype, and who had given their consent to donate a cell sample to the biobank during follow-up in the Adult Down Syndrome Unit between 2016 and 2018. No specific exclusion criteria were used.

Study variables

All data were collected retrospectively from the participants' medical records. In the Comunidad de Madrid, all medical records for each patient both from public (i.e. state-owned) primary care clinics and hospitals are merged into a single portal (HORUS). This portal is a clinical tool that covers all individuals with a Social Security number in the region of Madrid. As such, it includes demographic and health information on a vast majority of individuals in this region. Data are partly entered by their general practitioners and other specialists in the public health system and partly automatically from test results and electronic prescriptions. This variability in the source of the information allows some objective data to be obtained in detail, such as medication use, and others less consistently, such as co-morbidities, as their inclusion depends on the thoroughness of each input. Portal access and data confidentiality is controlled by the Comunidad Autónoma de Madrid's Health Department and is regulated by current Spanish legislation (BOE-A-2018-16673 Ley Orgánica 3/2018, 2018). Demographic (age, sex and ethnicity) and clinical information were obtained, including the following conditions: congenital heart disease, obstructive sleep apnoea, hypothyroidism, hearing and visual deficits, epilepsy and mental illness. Mental illness was defined according to ICD10 criteria. Finally, other co-morbidities – any acute or chronic physical illness requiring treatment/intervention – were categorised under one common variable. The use of psychotropic medication at inclusion was also recorded for all participants, which included antidepressants, neuroleptics or anxiolytics taken at the time of recruitment into the study.

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All infections and causes for admission, including those admissions in which a patient died, were recorded after review of the medical chart. The dates and causes of death were also collected. Vaccination against SARS-CoV-2 was available in Spain for people with DS from January 2021 for institutionalised individuals and from April 2021 for community-living adults, and the number of vaccine doses received were confirmed through a review of official vaccination certificates, which are directly recorded in the patients' primary care medical history. More detailed information on the variables included in the study can be found in the supporting information.

Patient and public involvement

Adults with DS were not involved in the design or conduct of the research. However, once the results have been published, they will be disseminated to participants and members of the Down syndrome community at large in an accessible format and language (suitable for lay readers) via dedicated websites of DS associations [Down España (https://www.sindromedown.net), Fundación Iberoamericana Down21 (https://www.down21.org)] and research societies [T21RS (https://www.t21rs.org), DSMIG-USA (https://dsmig-usa.org)].

Ethical aspects

The study was carried out in line with the principles of the Declaration of Helsinki (World Medical Association 2013) and current good clinical practice guidelines. Data confidentiality was guaranteed in line with current legislation. The institutional review board approved the study and the exemption from requesting informed consent owing to the absence of an intervention in the study population and the retrospective and anonymous nature of the study, where patients were only identified by their age.

Statistical analysis

The most appropriate sample size was not estimated, because the full sample of individuals meeting the inclusion criteria was used (see above). Checks were carried out prior to analysis to ensure data integrity and reliability, including data cleaning procedures, identification and resolution of missing values and verification of data accuracy. Mean and standard deviation were used to describe continuous variables and percentages for categorical variables. Deaths were classified as pre-pandemic if they occurred before 1 March 2020 and post-pandemic if they happened at a later date. Bonferroni method was used when *post hoc* multiple comparisons were made.

We conducted separate logistic regression analyses to investigate the relationship between potential predictors and the two distinct groups of deaths, categorised according to date (pre-pandemic and post-pandemic). In these analyses, we treated death as the dependent variable and used the clinical and demographic variables described in the previous sections as independent variables. All models included age and dementia as confounding factors because their association with risk of death is well known. Participants who died in the pre-pandemic period were excluded from the predictive models evaluating post-pandemic deaths.

In a second stage, the characteristics of individuals who died in the pre-pandemic and post-pandemic period were compared using Student's *t* test for continuous variables and chi-squared or Fisher's exact test in the case of categorical ones. Demographic variables (sex and origin) and clinical variables (intellectual disability, visual or hearing impairment, congenital heart disease, dementia, epilepsy, hypothyroidism, sleep apnoea, mental illness or use of psychotropic medication, among other co-morbidities) were analysed. Those factors with a statistical association of $P < 0.20$ in the univariate analysis were included in a multivariate logistic regression model to adjust for confounders. To select the final model, all possible subsets of the maximum model were compared, selecting the most parsimonious model in which the variation in odds ratio (OR) was not clinically significant (<10%) from the initial baseline model. All statistical tests were two-tailed, establishing a *P*-value of 0.05 as the cut-off for statistical significance. Data were processed using Stata software (Stata v15.0).

Results

Description of the study sample

Five hundred seventy-two adults participated in the study, with a mean age of 43.4 years (SD 11.8 years), 278 (48.6%) of whom were women. Most of them (532, 93.0%) had a mild–moderate baseline ID, while 17 (2.97%) were classified as severe or profound (23 participants lacked enough clinical data to be classified into a group, 4%). Of the total sample, 125 individuals (21.9%) were diagnosed with AD, 32 (5.6%) of whom were classified as MCI and 93 (16.3%) as dementia. Forty-one participants with AD had a concomitant diagnosis of epilepsy. A descriptive summary of the characteristics of this cohort is presented in Table 1.

Analysis of mortality causes and risk factors

Sixty-seven participants (11.7%) died during follow-up. The date of death of one person was unknown and thus excluded from the comparative analyses. Twenty individuals (3.5% of the total sample) died in the pre-pandemic period (from the beginning of the recruitment and follow-up in December 2016 to 29 February 2020) and 46 (8%) after the start of the pandemic (from 1 March 2020 until the end of follow-up on 26 October 2022). Age, dementia, epilepsy, visual impairment and the presence of co-morbidity were significantly associated with a higher risk of death, regardless of the study period considered.

As for the causes of death, 36/66 patients died due to respiratory infections, 3/66 to other infections and 9/66 to other causes. In 18/66 individuals, the cause of

Table 1 Descriptive characteristics of the study sample

		Alive (n = 505)	Deceased before the pandemic (n = 20)	Deceased since the pandemic (n = 46)	One-way ANOVA or χ^2 results	Adjusted p values of contrasts
Age (years)		42 (11)	57 (5.9)	57 (7.3)	$F_{(2,\ 568)} = 58.3$ $P < 0.001$*	$p_1 = 1.000$ $p_2 < 0.001$ $p_3 < 0.001$
Sex	Female	247 (49%)	10 (50%)	21 (46%)	$\chi^2_{(2)} = 0.19$ $P = 0.908$	$p_1 = 1.000$ $p_2 = 1.000$ $p_3 = 1.000$
Intellectual disability	Mild–moderate	469 (93%)	16 (80%)	46 (100%)	$\chi^2_{(2)} = 20.7$ $P = 0.003$**	$p_1 = 0.020$ $p_2 = 0.009$ $p_3 = 1.000$
	Severe–profound	13 (2.6%)	4 (20%)	0		
Alzheimer's disease	CS	434 (86%)	3 (15%)	10 (22%)	$\chi^2_{(4)} = 175.1$ $P < 0.001$*	$p_1 = 1.000$ $p_2 < 0.001$ $p_3 < 0.001$
	MCI	25 (5.0%)	1 (5.0%)	5 (11%)		
	Dementia	46 (9.1%)	16 (80%)	31 (67%)		
Age of dementia onset (years)		52 (4.9)	52 (4.2)	53 (6.5)	$F_{(2,121)} = 0.61$ $P = 0.544$	$p_1 = 0.674$ $p_2 = 0.988$ $p_3 = 0.565$
Epileptic seizures	No	474 (94%)	8 (40%)	30 (65%)	$\chi^2_{(2)} = 94.6$ $P < 0.001$*	$p_1 = 0.196$ $p_2 < 0.001$ $p_3 < 0.001$
	Yes	30 (5.9%)	12 (60%)	16 (35%)		
Smoking	No	502 (99%)	19 (95%)	46 (100%)	$\chi^2_{(4)} = 8.20$ $P = 0.221$	$p_1 = 0.303$ $p_2 = 0.144$ $p_3 = 1.000$
	Former smoker	2 (0.4%)	1 (5.0%)	0		
Congenital heart disease	No	390 (77%)	16 (80%)	38 (83%)	$\chi^2_{(2)} = 1.25$ $P = 0.575$	$p_1 = 0.725$ $p_2 = 1.000$ $p_3 = 0.349$
	Yes	114 (23%)	4 (20%)	7 (15%)		
Sleep apnoea	No	392 (78%)	17 (85%)	40 (87%)	$\chi^2_{(2)} = 2.69$ $P = 0.313$	$p_1 = 1.000$ $p_2 = 1.000$ $p_3 = 0.567$
	Yes	113 (22%)	3 (15%)	6 (13%)		
Hypothyroidism	No	191 (38%)	9 (45%)	17 (37%)	$\chi^2_{(2)} = 0.44$ $P = 0.801$	$p_1 = 0.591$ $p_2 = 0.640$ $p_3 = 1.000$
	Yes	314 (62%)	11 (55%)	29 (63%)		

Table 1. *(Continued)*

		Alive (n = 505)	Deceased before the pandemic (n = 20)	Deceased since the pandemic (n = 46)	One-way ANOVA or χ^2 results	Adjusted p values of contrasts
Mental illness	No	357 (71%)	10 (50%)	24 (52%)	$\chi^2_{(2)} = 9.98$	$p_1 = 1.000$
	Yes	148 (29%)	10 (50%)	22 (48%)	$P = 0.007$***	$p_2 = 0.234$
						$p_3 = 0.036$
Psychotropic medication	No	320 (63%)	10 (50%)	12 (26%)	$\chi^2_{(2)} = 25.2$	$p_1 = 0.263$
	Yes	185 (37%)	10 (50%)	34 (74%)	$P < 0.001$***	$p_2 = 0.731$
						$p_3 < 0.001$
Visual impairment	No	390 (77%)	10 (50%)	24 (52%)	$\chi^2_{(2)} = 20.5$	$p_1 = 1.000$
	Yes	114 (23%)	10 (50%)	22 (48%)	$P < 0.001$*	$p_2 = 0.036$
						$p_3 = 0.001$
Hearing impairment	No	454 (90%)	16 (80%)	35 (76%)	$\chi^2_{(2)} = 10.9$	$p_1 = 1.000$
	Yes	47 (9.3%)	4 (20%)	11 (24%)	$P = 0.005$***	$p_2 = 0.122$
						$p_3 = 0.005$
Other co-morbidities	No	131 (26%)	0	4 (8.7%)	$\chi^2_{(2)} = 13.4$	$p_1 = 0.918$
	Yes	374 (74%)	20 (100%)	42 (91%)	$P < 0.001$*	$p_2 = 0.018$
						$p_3 = 0.021$

CS, cognitively stable/no cognitive impairment; MCI, mild cognitive impairment. Bonferroni test was used for multiple comparisons. Contrasts are arranged as follows: p_1 = pre-pandemic versus post-pandemic; p_2 = alive versus pre-pandemic; p_3 = alive versus post-pandemic. The number of asterisks (*) refers to the result of *post hoc* binary comparisons corrected by the Bonferroni method.

*No significant differences between pre and post-pandemic deaths.

**No significant differences between post-pandemic deaths and alive participants.

***Only significant differences between post-pandemic deaths and alive participants.

death was unknown, either not recorded or unable to be ascertained after review of the patients' medical records (25% and 28.3% of the deaths in the pre-pandemic and post-pandemic periods, respectively). Of those deaths related to respiratory infections, 9/20 (45.0%) occurred in the pre-pandemic period and 27/46 (58.7%) after the start of the pandemic. The most frequent mechanisms of respiratory infection were COVID-19 pneumonias (15/66, 22.7% of the deaths) and aspiration pneumonias (12/66, 18.2%). A more detailed list of these causes can be found in Table S1A,B.

Once adjusted for age and dementia, we found a statistically significant association between pre-pandemic mortality and the following variables: severe–profound ID [OR 15.8, 95% confidence interval (CI) 3.29–76.0] and epilepsy (OR 5.87, 95% CI 2.09–16.4), as factors that increased the risk of death; and age of onset of AD symptoms, which showed a negative correlation with mortality (the lower the age of onset, the higher the risk of death; OR 0.79, 95% CI 0.65–0.96). In the post-pandemic mortality analysis, epilepsy (OR 3.39, 95% CI 1.46–7.86) and age of onset of dementia (OR 0.78, 95% CI 0.66–0.93) showed a similar correlation pattern to that previously observed. However, we also found that psychotropic medication was a risk factor for mortality (OR 2.24, 95% CI 1.04–4.82). Furthermore, although no association between death and COVID-19 was demonstrated (OR 1.10, 95% CI 0.54–2.23), vaccination against COVID-19 was shown to have a very strong protective effect on post-pandemic mortality, decreasing the risk of dying by 95% (OR 0.0002, 95% CI 6.7e10^{-6} to 0.004; relative risk calculated with marginal estimates: 0.05, 95% CI 0.03–0.09; see Fig. 1 and Table 2 for more information).

Comparative analysis between pre-pandemic and post-pandemic deaths

When the clinical profile of pre-pandemic and post-pandemic deaths was compared, only significant differences in the distribution of the groups according to their degree of ID (it was not severe in any of the deceased since the beginning of the pandemic) were observed. Differences at the limit of statistical significance were detected for epilepsy (more frequent

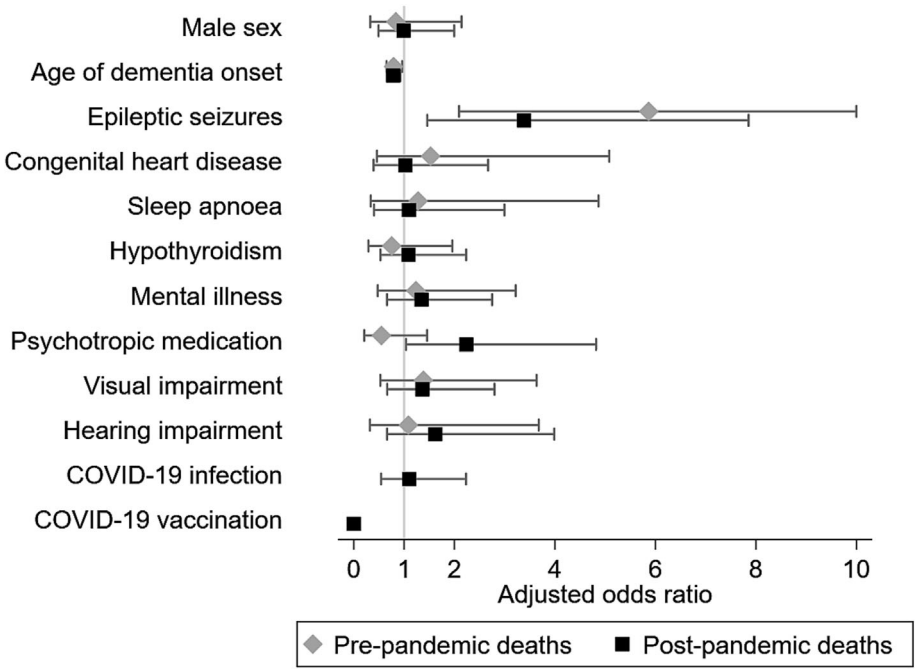

Figure 1. Predictive factors for death in individuals with Down syndrome before and after the onset of the COVID-19 pandemic (adjusted for age and dementia).

Table 2 Predictive factors for death (adjusted for age and dementia) before and after the onset of the COVID-19 pandemic

Variables	Pre-pandemic OR (95% CI)	Post-pandemic OR (95% CI)
Male sex	0.84 (0.33–2.14); $P = 0.708$	0.99 (0.49–2.00); $P = 0.976$
Severe-profound intellectual disability	15.8 (3.29–76.0); $P = 0.001$**	-
Age of dementia onset	0.79 (0.65–0.96); $P = 0.019$*	0.78 (0.66–0.93); $P = 0.004$**
Epileptic seizures	5.87 (2.09–16.4); $P = 0.001$**	3.39 (1.46–7.86); $P = 0.004$**
Former smoker	18.40 (0.94–359.9); $P = 0.055$	-
Congenital heart disease	1.53 (0.46–5.08); $P = 0.490$	1.02 (0.39–2.67); $P = 0.963$
Sleep apnoea	1.28 (0.34–4.87); $P = 0.719$	1.10 (0.40–3.00); $P = 0.859$
Hypothyroidism	0.75 (0.29–1.96); $P = 0.562$	1.09 (0.53–2.23); $P = 0.820$
Mental illness	1.23 (0.47–3.22); $P = 0.666$	1.35 (0.66–2.75); $P = 0.414$
Psychotropic medication	0.55 (0.21–1.46); $P = 0.228$	2.24 (1.04–4.82); $P = 0.040$*
Visual impairment	1.38 (0.53–3.64); $P = 0.509$	1.36 (0.66–2.80); $P = 0.400$
Hearing impairment	1.08 (0.32–3.68); $P = 0.896$	1.62 (0.66–3.99); $P = 0.291$
Co-morbidities	-	1.09 (0.33–3.57); $P = 0.888$
COVID-19 infection	-	1.10 (0.54–2.23); $P = 0.793$
COVID-19 vaccination	-	0.0002 ($6.7e10^{-6}$ to 0.004); $P < 0.001$**

*Statistical significance at $P < 0.05$.
**Statistical significance at $P < 0.01$.

in the pre-pandemic group; $\chi^2(1) = 3.63$; $P = 0.057$) and for the use of psychotropic medication (preponderant in the post-pandemic group; $\chi^2(1) = 3.59$; $P = 0.058$). No significant differences were demonstrated for any other relevant variables, including age of death, AD stage, age of dementia onset or other co-morbidities. In fact, we explored the distribution of the age of death as a function of the date at which it occurred, finding an accumulation of deaths coinciding with the onset of the pandemic, with a slightly positive correlation – although not significant – in the linear prediction (for each year of follow-up, the age at death increased 0.03 years; $F_{1, 63} = 2.01$, $P = 0.161$), as shown in Fig. 2.

In the multivariate analysis comparing deaths in both periods, the use of psychotropic medication was the only factor significantly associated with post-pandemic deaths with respect to the pre-pandemic period (OR 5.26; 95% CI 1.38–20.1; $P = 0.015$).

Discussion

We have not found significant overall differences in the clinical characteristics and the factors that increase mortality in a cohort of adults with Down syndrome before and after the onset of the COVID-19 pandemic. In fact, contrary to the initial hypothesis, the age at death continued to increase slightly in the post-pandemic period. Although the COVID-19 pandemic has undoubtedly had a considerable impact on mortality in its first waves, the previous trend of a progressive increase in life expectancy observed in the DS population seems to have recovered thereafter.

The use of psychotropic medication was the only differential factor in both groups that was significantly associated with an increase in the risk of death in the post-pandemic phase. This finding is consistent with other studies showing an association between pre-existing mental disorders, exposure to antipsychotics and anxiolytics, and COVID-19 mortality (Vai *et al.* 2021; Descamps *et al.* 2022). There could be several explanations for this fact. We cannot rule out that the association may be biased by the presence of other factors that were not adequately measured, such as the severity of mental illnesses, which were all grouped together under a single category in a binary variable. However, it is known that the prevalence of mental health issues in the general population increased after the pandemic (Wang *et al.* 2020; Kwong *et al.* 2021; Luijten *et al.* 2021; Prieto *et al.* 2021; Fountoulakis *et al.* 2022). Subsequently, psychotropic medications might have become more widely prescribed, especially in a context of a more restricted access to health care services. Second, psychotropic

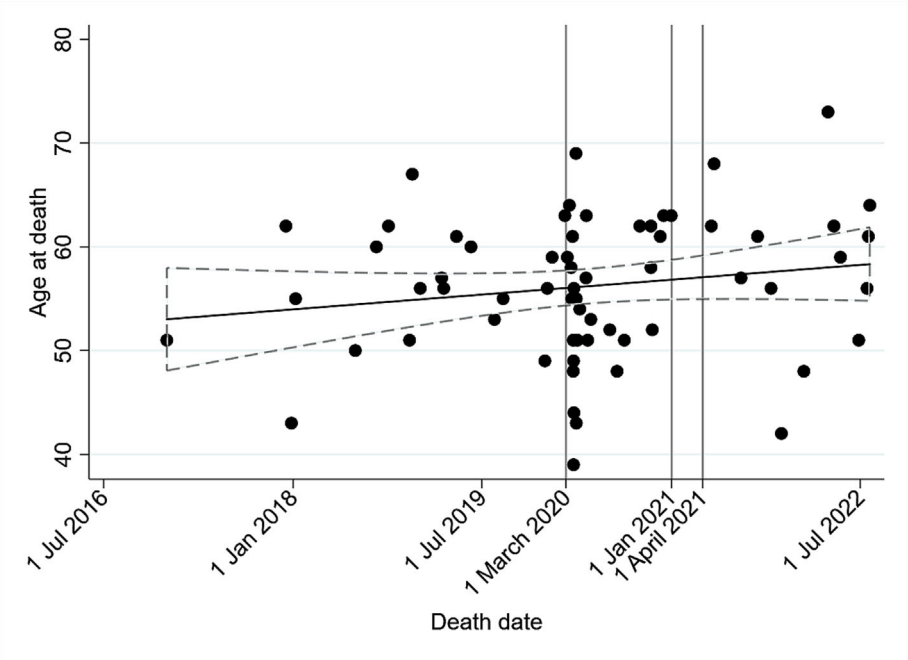

Figure 2. Distribution of deaths in the study sample over the follow-up period. March 2020 has been marked as the theoretical start of the COVID-19 pandemic. Vaccines were available in Spain for people with Down syndrome from January 2021 for institutionalised individuals and from April 2021 for adults living in the community.

medications also influence the prognosis of respiratory infections. In the general population, several psychotropic drugs, used for dementia, depression, pain or insomnia, including benzodiazepines, have been identified as risk factors for pneumonia, especially in people with AD (Rajamaki *et al.* 2020). In addition, many psychotropic medications pose relevant interactions with treatments commonly used against COVID19, increasing the rate of potential side effects (Javelot *et al.* 2020). Third, it has been suggested that patients with mental disorders have had less access to life-saving measures during the peak of the pandemic (Schwarzinger *et al.* 2023).

The other relevant finding from our study is that vaccination against COVID-19 behaves as a very potent protective factor against death. Indeed, it is possible that we were not able to find an association between COVID-19 infection and mortality due to the buffering, protective effect of vaccination in the post-pandemic period. Although we did not analyse separately the periods before and after the vaccine became available in Spain in the first months of 2021, the graphical representation of the temporal distribution of deaths (Fig. 2) shows a decrease in deaths coinciding with these dates. Furthermore, the faulty coding of a relevant proportion of deaths observed in our study might have watered down a still more robust association between vaccination and mortality. This protective effect had been well documented in the general population but had not been yet confirmed in people with DS, in whom the efficacy of the vaccine was initially questioned due to their immune dysregulation (Joshi *et al.* 2011; Majithia & Ribeiro 2022; Esparcia-Pinedo *et al.* 2023). Though mRNA vaccines are highly effective in reducing the mortality rate by up to 97% in the general population (Gómez Marco *et al.* 2021), the risk of dying remains higher in older people or those with co-morbidities such as obesity, hypertension or diabetes and DS (Scruzzi *et al.* 2022; Esparcia-Pinedo *et al.* 2023). However, in our study, after adjusting for potential confounders and co-morbidities, vaccination still reduced their relative risk of death by 95%.

Ours is one of the largest published clinical cohorts of adults with DS, which included the entire spectrum of intellectual disability and AD, usually difficult to

represent in research studies. The low representation of individuals with severe and profound ID in our sample could have been due to their less frequent involvement in research projects and/or blood sample donations (which was the main inclusion criterion in our cohort). Furthermore, though several studies have analysed the impact of COVID19 on mortality in adults with DS (Clift *et al.* 2021; Hüls *et al.* 2021; Real de Asua *et al.* 2021; Williamson *et al.* 2021; Koyama *et al.* 2022; Lunsky *et al.* 2022), we are not aware of any study that has analysed the differences in the profile of deaths between the pre-pandemic and post-pandemic phases. In light of our results, special consideration needs to be given to the prescription and use of psychotropic medication among adults with DS. This is particularly relevant among adults with DS and dementia, in whom this prescription, as well as the presence of possible deleterious side effects, might be most frequent. Secondly, our results reinforce those of prior studies that insisted on the imperative need to actively vaccinate this sector of the population.

We cannot overlook some limitations of our study, mainly the sample selection, which was not random, but based on the availability of biological samples in the institutional biobank. This fact could have led to a selection bias that could limit the generalisability of the results, especially considering that this is a hospital-based cohort. As an additional drawback, the clinical variables were recorded from the information available in the medical records, without direct access to the death certificates, which could have reduced the reliability of the data. Consequently, in up to 27% of cases, the cause of death was unknown or not correctly recorded, which should be taken into account when interpreting our results. This also meant that in many cases, it was not possible to collect data on isolated co-morbidities, such as obesity or diabetes. Previous research by our group did not find an association between these co-morbidities and COVID-related mortality (Real de Asua *et al.* 2021), and the exclusion of these variables does not diminish the need for future research to explore the specific associations between metabolic disorders, risk of infection and mortality in individuals with Down syndrome. Furthermore, because the information was collected retrospectively and coded by the researchers without direct involvement of the physicians who first treated the participants, we cannot rule out the possibility that some of the variables may have been miscoded, such as the degree of dementia or the causes of respiratory infection. Baseline ID level and AD stage were estimated using subjective information provided by caregivers and indirect data from clinical assessments, which is an important limitation in the accuracy of these categorisations. This problem could be addressed in future studies incorporating such validated measures with functional assessments, prospectively. Finally, the inclusion of a single cohort for comparison between the two groups according to their date of death introduces the possibility of survival bias in our study, which could affect the generalisability and robustness of our conclusions. Further research using longitudinal designs and different cohorts would be valuable to provide a more complete understanding of mortality patterns in people with Down syndrome, while taking into account survivor effects.

In summary, we can conclude that our study reveals that the emergence of COVID-19 has not affected the previous trend of progressive increase in life expectancy of adults with DS in our country, which supports that they are receiving adequate care, especially through preventive actions such as their prioritisation in vaccination campaigns. Nevertheless, we should continue to be alert to minimise the possible harm caused by other medical interventions, such as the prescription of psychotropic medication. Given the correlation observed between their use and higher mortality rates, a call for a more judicious use of these drugs cannot be overstated.

Author contributions

Project coordination, original idea: BS and DRA. Subject recruitment and follow-up: LA. Database compilation: BS, LA and JR. Statistical analysis: BS. Results evaluation, manuscript drafting and approval of the final version: All.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. Description of the causes of death of the study participants.
Table S2. Dictionary of variables.