

# Excess mortality and years of life lost from 2020 to 2023 in France: a cohort study of the overall impact of the COVID-19 pandemic on mortality

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#### **ABSTRACT**

Introduction Excess mortality has been frequently used worldwide for summarising the COVID-19 pandemic-related burden. Estimates for France for the years 2020–2022 vary substantially from one report to another, and the year 2023 is poorly documented. The present study assessed the level of excess mortality that occurred in France between 2020 and 2023 together with the corresponding years of life lost (YLL), in order to provide a reliable, detailed and comprehensive description of the overall impact of the pandemic.

**Method** This open cohort study of the whole French population analysed the 8 451 372 death occurrences reported for the years 2010–2023. A Poisson regression model was trained with years 2010–2019 for determining the age-specific and sex-specific evolution trends of mortality before the pandemic period. These trends were then used for estimating the excess mortality during the pandemic period (years 2020–2023). The life expectancies of the persons in excess mortality were used for estimating the corresponding YLL.

**Results** From 2020 to 2023, the number of excess deaths (mean (95% CI) (percentage of change versus expected mortality)) was, respectively, 49 541 (48 467; 50 616) (+8.0%), 42 667 (41 410; 43 909) (+6.9%), 53 129 (51 696; 54 551) (+8.5%), and 17 355 (15 760; 18 917) (+2.8%). Corresponding YLL were 512 753 (496 029; 529 633), 583 580 (564 137; 602 747), 663 588 (641 863; 685 723), and 312 133 (288 051; 335 929). Individuals younger than 60 years old accounted for 17% of the YLL in 2020, 26% in 2021, 32% in 2022 and 50% in 2023. Men were more affected than women by both excess mortality and

**Conclusion** This study highlights the long-lasting impact of the pandemic on mortality in France, with four consecutive years of excess mortality and a growing impact on people under 60, particularly men, suggesting lasting and profound disruption to the healthcare system.

## INTRODUCTION

The COVID-19 pandemic quickly spread worldwide in 2020. According to the WHO, the pandemic cumulative direct death toll on 31 December 2023 was 7015947 deaths.<sup>1</sup>

#### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Different trends and magnitudes of excess mortality were reported in France for the years 2020–2022, and estimations of years of life lost, which characterise the remaining life expectancy of people suffering excess mortality, are only available for 2020 and 2021. There is no exhaustive toll covering all years of the COVID-19 pandemic period (2020–2023).

#### WHAT THIS STUDY ADDS

⇒ Excess mortality peaked in 2022 and remained substantial in 2023 for the fourth year in a row while corresponding years of life lost rose steadily from 2020 to 2022 and remained at a worrying level in 2023.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study raises concerns about a potential indirect and long-lasting impact of the COVID-19 pandemic on mortality in France, particularly in men under 60 years old.

Excess mortality, defined as the difference between observed and expected mortality, constitutes an attractive feature for summarising the major impact of the pandemic, for at least two reasons. First, estimating excess mortality only requires all-cause mortality data during a reference period and during the pandemic period of interest, which is advantageous given potential inconsistencies and non-uniformity in cause-of-death classification across time and regions.<sup>2</sup> Second, excess mortality is a straightforward estimate of the global burden, including both virusrelated direct deaths and indirect deaths related to all perturbations that simultaneously occurred during the pandemic period. Thanks to its relevancy, excess mortality has rapidly become an essential indicator for assessing the impact of the pandemic.<sup>3</sup> As detailed by Vanella et al in their review article,

the concept of excess mortality initially emerged in 1930 and called particular renewed attention during the COVID-19 pandemic. $^4$ 

Numerous studies have already estimated excess mortality in France between 2020 and 2021 with heterogeneous results. This heterogeneity is inducted by different assumptions and methodological choices, 5-8 as illustrated in the study of Levitt et al, which details the differences between final estimates issued from four major contributions (the COVID-19 Excess Mortality Collaborators, 10 Karlinsky and Kobak, 11 The Economist team 12 and WHO<sup>13</sup>): in France, estimates vary almost threefold, from 57767 to 155000 excess deaths in 2020 and 2021. Considering the year 2022, all sources agreed about the maintenance of some excess mortality, but with relative estimates contrasting substantially: The French National Institute for Statistic and Economic Studies (Insee) estimated that excess mortality in 2022 was greater than its corresponding estimates for the two previous pandemic years, 14 while in contrast, Eurostat and the European Mortality Monitoring Project estimated that it was lower than in 2020. 15 16 All these results demonstrate a high variability of estimates depending on methodological choices and raise questions about the real level of excess mortality in France and its evolution during the pandemic period. Concerning 2023, while WHO declared that COVID-19 no longer constituted a public health emergency of international concern (PHEIC), 17 no official estimation of excess mortality in France is published to our knowledge. Furthermore, while excess mortality is a good summary indicator, it provides insufficient information to fully quantify the burden linked to the pandemic since, as underlined by Ferenci, 18 raw death counts do not acknowledge the age of the deceased persons. A few studies have already investigated the numbers of years of life lost (YLL) related to the pandemic, 19 20 but little is known after 2020.

To sum up, there is a wide range of estimates of excess mortality in France from 2020 to 2022, no official figures for 2023 and a lack of detail on the age and sex structure of people affected after 2020. To address these issues, the study reported here had three objectives.

The first objective was to accurately estimate excess mortality, taking into account changes in population structure over time and natural trends in mortality, in order to shed light on the exact level of excess mortality in France between 2020 and 2022. The second objective was to estimate the level of excess mortality in 2023, in order to assess whether the situation is returning to normal after three consecutive years of increased mortality. The third objective was to estimate the YLL between 2020 and 2023, taking into account the age and sex of those in excess mortality in the balance sheet. By simultaneously addressing these three objectives, the overall aim of the study was to draw up a complete assessment of the pandemic burden in France, from the year of the emergence of COVID-19 in 2020 to the year WHO declared the end of the PHEIC.

## **MATERIALS AND METHODS**

#### Data source and availability

All data used in the study are available in open access from the French National Institute for Statistic and Economic Studies (Insee), including daily mortality by age and sex, <sup>21</sup> population structure <sup>22</sup> and mortality tables. <sup>23</sup>

## **Participants**

The present open cohort study of the whole French population between 2010 and 2023 is reported according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines. A sensitivity analysis including only metropolitan departments was performed in online supplemental text 1. Throughout the study, the term 'sex' refers to the sex assigned at birth. In accordance to the Sex and Gender Equity in Research guidelines, sex was precisely taken into account in the model, and the results were detailed by sex. In the above-mentioned databases, the population size by age and sex at a given year considers the situation on January 1.

## **Data processing**

As the age structure of the French population is given on January 1 of each year, the age of a deceased person considered in the study was that on January 1 of the year of death, and mortality data were aggregated by year. Persons aged 99 years or more were handled in a single age category and individuals who died outside France were not included in the study. Given that in France the legal deadline for transmitting death certificates to INSEE is 1 week, <sup>26</sup> and that the extraction of mortality data dates from June 2024, the number of missing data between 2010 and 2023 should be minimal.

## **Outcomes**

For each sex i, age j and year k, expected mortality  $(E\left[\text{Mortality}_{ijk}\right])$  was estimated with a Poisson regression model described next. The numbers of excess deaths  $(\hat{D}_{ijk})$  were estimated for each stratum by subtracting the expected mortality from the observed one.  $\hat{D}_{ijk} = M_{ijk} - E$  For a given year, the total burden is the sum of the agespecific and sex-specific excess deaths, for example

$$\hat{D}_{2020} = \sum_{i \in \{\text{men, women}\}} \sum_{j=0}^{99} \hat{D}_{i,j,2020}$$

YLL were estimated by multiplying each estimated excess death by the corresponding life expectancy ( $E_{ijk}$ ), based on the mortality table of 2019.<sup>23</sup> YLL<sub>ijk</sub> =  $\hat{D}_{ijk} \times E_{ijk}$ . The estimate of the total burden for a given year is the sum of the age-specific and sex-specific YLL. A sensitivity analysis with a fixed cut-off of 80 years old was done in online supplemental text 1.

## Statistical model and selection process

We used a Poisson regression model to calculate expected mortality in the pandemic period (years 2020–2023), with years 2010–2019 handled as the reference period. Such models have already been used to estimate the



expected level of mortality in order to estimate excess cause-specific<sup>27</sup> or all causes excess mortality.<sup>28</sup> <sup>29</sup>

Age (as a year-specific categorical variable), sex and year (as a continuous variable) were used as predictors to estimate mortality. Different interactions of these variables were tested, and Akaike Information Criterion (AIC) was used as selection criteria to optimise goodness-of-fit and avoid overfitting (online supplemental table 1). Fitting by age, year and sex was visually assessed in online supplemental figure 1. Sensitivity analyses were conducted to (1) evaluate the performances of a model with weekly resolution including a cyclic spline, aimed at capturing seasonal periodicity and a long-term trend spline among explanatory variables, and (2) explore the influence of the reference period length (see online supplemental text 1, online supplemental figure 2, and online supplemental figure 3). Details of the model selection are given in online supplemental text 2 and online supplemental figure 4. The model selected was

$$\begin{split} \log \left( E\left[ \text{Mortality}_{ijk} \right] \right) &= \log \left( \text{Population}_{ijk} \right) + \beta_0 + \beta_1 \cdot \text{Sex}_i + \beta_2 \cdot \text{Age}_j + \beta_3 \cdot \text{Year}_k \\ \\ &+ \beta_4 \cdot \text{Sex}_i \cdot \text{Age}_j + \beta_5 \cdot \text{Sex}_i \cdot \text{Year}_k + \beta_6 \cdot \text{Age}_j \cdot \text{Year}_k + \beta_7 \cdot \text{Sex}_i \cdot \text{Age}_j \cdot \text{Year}_k \end{split}$$

This model allowed us to accurately estimate age-specific and sex-specific expected number of deaths, excess mortality and corresponding YLL, considering mortality trends and changes in population structure over time.

#### Software, packages, code and estimation of CIs

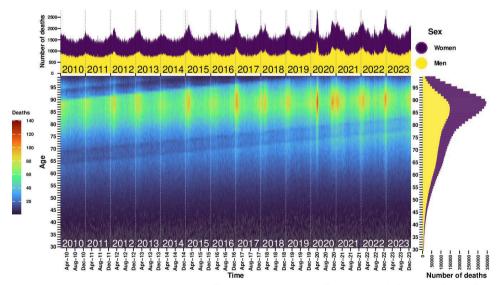
All analyses were performed with statistical software R V.4.0.2 (R Foundation for Statistical Computing, Vienna, Austria), package ggplot2 was used to generate figures, package stats was used for the general linear model, and 95% CIs were estimated over 10000 bootstrap replications. The use of the viridis colour palette in the graphs was based on its perceptual uniformity and colourblind

friendliness to ensure accurate data interpretation and broad accessibility. The R code used to perform the analyses in this paper is openly available at https://github.com/Paulm2520/excess\_mortality\_code.

#### **RESULTS**

## **Population under study**

Between 2010 and 2023, the French population grew from 64.6 million to 68.1 million inhabitants, and the corresponding observations included in the study totalised 931741878 person-years (see study flow diagram in the online supplemental figure 5). Over the analysis period, 8536511 deaths occurred, of which less than 1% were not considered because they took place abroad. The study was therefore based on 8451372 deaths to estimate excess mortality and YLL. A graph plotting the raw mortality events occurring during the study period already documents substantially some mortality patterns in France over time: figure 1 shows the presence of periodical patterns of mortality, with higher levels usually observed during winters, reflecting, at least in part, the impact of seasonal-circulating viruses such as influenza. Moreover, the figure also evidences the impact of population structure on crude mortality over time. The two dark diagonal stripes (in 2010: one beginning between 64 and 69 years old, and one between 91 and 94 years old) showing lower mortality levels correspond to two particular cohorts, persons born in 1939-1945 (second world war) and 1914-1918 (first world war). During these two periods, natality was low, inherently resulting in cohorts with smaller sample sizes and a corresponding lower crude mortality over time. Impact of the COVID-19 pandemic is also flagrant in 2020 with, for instance, the especially high mortality in April, followed by a succession



**Figure 1** Daily mortality by age, and repartition by sex, France, 2010–2023. Top panel, daily mortality in France from 2010 to 2023 with the repartition by sex; right panel, cumulative number of deaths by exact age from 30 to 99 years old with the repartition by sex; bottom panel, daily number of deaths according to exact age, for instance, in April 2020 the colour gradient is red for people between 85 and 90 years old corresponding to a daily number of deaths around 140 and this mortality peak is also visible in the top panel both for men and women.

of disturbances, until 2023 (see also online supplemental figure 6 that displays trends of mortality over time independently of changes in population structure).

## **Excess mortality**

A total of 162 692 (159 951; 165 335) excess deaths were estimated from 2020 to 2023 with 60% occurring in men. The estimated number of excess deaths (mean (95% CI)) was 49 541 (48 467; 50 616) in 2020, decreased to 42 667 (41 410; 43 909) in 2021, reached a maximum value in 2022 with 53 129 (51 696; 54 551) deaths, before dropping to 17 355 (15 760; 18 917) deaths in 2023 (table 1). As compared with the expected numbers of deaths, the aforementioned numbers of excess deaths in years 2020-2023 corresponded to increases of 8.0%, 6.9%, 8.5% and 2.8%, respectively. Figure 2 and the upper part of table 1 also provide insights on the variability of excess mortality over years 2020-2023, and according to sex. Variation of excess mortality between 2020 and 2022 was driven by women: excess mortality in men was almost as the same level during this period, while that in women dropped in 2021 before peaking in 2022. In 2023, excess mortality mainly affected men, with more than twice as many excess deaths as women. As shown in figure 2, excess mortality principally affected individuals older than 60 years, but a signal is also visible in men under 60 years. As detailed in the online supplemental table 2, individuals in excess mortality were younger in 2021 and 2023 (median ages of 78 and 76 years old, respectively), as compared with 2020 and 2022 (median ages of 83 and 81 years old).

## Years of life lost

From 2020 to 2023, the estimated total number of YLL related to excess deaths was 2 072 054 (2 030 339; 2 113 188) among which 64% concerned men. As detailed in the lower part of table 1, the overall level steadily rose from 512 753 (496 029; 529 633) in 2020 to 663 588 (641 863; 685 723) in 2022, before dropping to 312 133 (288 051; 335 929) in 2023. Despite men having a lower life expectancy than women at the same age, the estimated contribution of men to excess death-related YLL during the years 2020-2023 was always greater than that of women, particularly in 2023. Individuals in excess mortality were younger in 2021 and 2023 than in 2020 and 2022, resulting in a greater median number of YLL per individual in 2021 (11.2 years) and 2023 (13.1 years) than in 2020 (8.5 years) and 2022 (9.8 years). The contribution of individuals younger than 60 years old to the annual toll of excess mortality-related YLL dramatically rose over time, from 17% in 2020 to 50% in 2023, mainly driven by men from 20 to 60 years old (figure 3, online supplemental table 2 and figure 7).

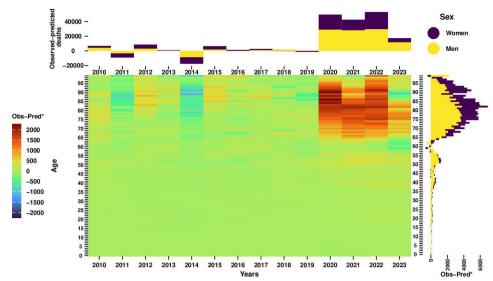
## **DISCUSSION**

## **Main findings**

In the present study, excess mortality and corresponding YLL from 2020 to 2023 in France were accurately assessed by considering in the modelling approach both the

Table 1 Excess	Table 1         Excess mortality and corresponding years of life lost by sex, France, 2020–2023	life lost by sex, France, 2020–2023		
Year	2020	2021	2022	2023
Excess mortality*	49 541 (48 467; 50 616) (+8.0%)	42 667 (41 410; 43 909) (+6.9%)	53 129 (51 696; 54 551) (+8.5%)	17 355 (15 760; 18 917) (+2.8%)
Men	28 925 (28 164; 29 677) (+9.4%)	28 070 (27 209; 28 839) (+9.2%)	29 572 (28 578; 30 566) (+9.6%)	11 623 (10 512; 12 741) (+3.8%)
Women	20 616 (19 841; 21 402) (+6.6%)	14 597 (13 706; 15 465) (+4.7%)	23 557 (22 545; 24 575) (+7.5%)	5 732 (4 589; 6 847) (+1.8%)
Years of life lost†	512 753 (496 029; 529 633)	583 580 (564 137; 602 747)	663 588 (641 863; 685 723)	312 133 (288 051; 335 929)
Men	319 011 (306 331; 331 834)	389 059 (374 698; 403 427)	398 672 (382 659; 414 739)	213 911 (196 033; 231 583)
Women	193 742 (182 580; 205 027)	194 521 (181 692; 207 371)	264 916 (250 489; 279 666)	98 222 (81 989; 114 361)

Excess mortality (95% CI)(percentage of increase compared with expected mortality). †Years of life lost (95% CI).



**Figure 2** Differences between observed and predicted deaths in France, 2010–2023. \*Observed minus predicted number of deaths. Top panel, annual cumulative difference between observed and predicted deaths, training period 2010–2019, with the repartition by sex; right panel, cumulative difference between observed and predicted deaths by exact age and according to sex from 2020 to 2023; main panel, annual difference between observed and predicted deaths by exact age, for instance, in 2020, the colour gradient is dark red for people aged 90 years old, corresponding to a difference between observed and predicted number of deaths at about 2000; this difference was considered as excess mortality as the baseline is estimated in prepandemic period and corresponds to mortality level in the absence of pandemic.

evolving trend of mortality over the 10 last years preceding pandemic, and the changes of population structure over time. In our study, we estimated 49 541 excess deaths for 2020, which is slightly higher than the 43 500 excess deaths estimated by Islam *et al.*<sup>30</sup> However, this study used a 4-year reference period, and as shown in online supplemental material, using a shorter reference period may

lead to an underestimation of excess mortality. Regarding 2020 and 2021, the 92 208 excess deaths estimated in our study align with published estimates, including the 81 849 excess deaths estimated by the WHO and the 96 831 excess deaths estimated by Levitt. For 2022, our estimate of 53 129 excess deaths closely matches the 53 800 excess deaths estimated by Insee. These comparisons

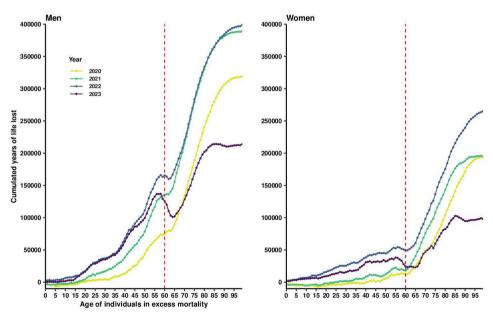


Figure 3 Cumulated number of years of life lost per age of individuals in excess mortality. For each year (colour) and each sex (panel), the points represent the cumulated number of years of life lost for individuals in excess mortality from 0 year old to the corresponding age. For instance, in 2020 (yellow line), men (left panel) younger than 60 years old (red dotted line) cumulated 73 000 years of life lost, around 23% of the 319 000 YLL cumulated by men in excess mortality in 2020. Cumulated number of YLL is decreasing when observed number of deaths in a particular stratum is below the expected one (negative excess mortality) as for instance in 2023 for individuals aged 60 years old. Contribution of each age to YLL is detailed in online supplemental figure 7.

confirm that the level of excess mortality was higher in 2022 than in 2020 and 2021. The present study estimated the occurrence of 17355 excess deaths in 2023, much less than the estimates for the three previous years. Despite the decline in the number of excess deaths estimated in 2021, the number of YLL constantly increased from 2020 to 2022, supporting the importance of considering the age distribution of the excess deaths. Individuals in excess mortality in 2021 were younger than those in 2020, but the balance between the lower number of deaths of individuals and their greater remaining life expectancies globally yielded a greater number of YLL. The same rationale explains that despite a slightly lower number of excess deaths observed in 2023 as compared with the three previous years, the number of YLL remains high because the mean age of excess deaths was the lowest of the pandemic period, and the individuals in excess mortality had a mean remaining life expectancy of more than 13 years. Over the course of the pandemic, people aged less than 60 years old accounted for a growing part of the total burden, starting from less than 20% in 2020 up to 50% in 2023, attesting for a major impact of the pandemic not only on older people, but also on persons from 20 to 60 years old, particularly men.

The burden of the pandemic increased in France from 2020 to 2022, when considering both the occurrences of excess deaths and corresponding ages. Despite a decline in 2023, the global burden of excess mortality remained substantial and affected younger people than in previous years, mostly in the male population, yielding a high number of YLL. The occurrence of four consecutive years of excess mortality reported in this study builds an unprecedented picture: indeed, after a major episode of excess mortality, one might expect a drop in the following year(s), as was observed for instance in France, when considering the 15000 excess deaths related to the 2003 heat wave, followed by a 23000 drop of deaths in 2004.31 However, unlike the COVID-19 pandemic, the 2003 heat wave was a short-term event that did not significantly disrupt healthcare systems or lead to delays in the management of acute and chronic conditions.

## **Implications**

Our study sheds light on the impact of the pandemic on mortality in France between 2020 and 2023. Investigating the causes of the increase over time evidenced in the study is of primary importance. Indeed, the co-occurrence in 2022 of critical features such as the achieved deployment of vaccination should have likely favoured a decreased burden as compared with earlier pandemic subperiods. Actually, the mortality directly attributed to COVID-19 decreased over time during the pandemic period, with deaths officially attributed to COVID-19 of 69 000, in 2020, <sup>32</sup> 60 895 in 2021, <sup>33</sup> 38 310 in 2022 and 5572 in 2023. <sup>34</sup> Opposed time trends between excess mortality estimated in the present study and the real dynamics of the COVID-19 threat (including the progressive immunity of the population protection after

exposure and vaccination) suggest that indirect consequences of the pandemic, such as long-term effects on the healthcare system organisation, may have contributed to increased mortality in 2022 and 2023. Numerous studies documented various critical pandemic-related changes in terms of health services: significant drops in hospitalisations for other causes than COVID-19.3536 delay or suspension of chronic disease management,<sup>37</sup> and delayed cancer diagnosis<sup>38</sup> likely leading to decreases in the long-term survival in these vulnerable subpopulations.<sup>39</sup> Other indirect contributions of the pandemic period may be thought of. For example, the earliest period of the pandemic was associated with a massive decrease in the circulation of seasonal respiratory viruses such as influenza, 40 whereas in 2022, France experienced a particularly high burden with two waves of influenza, one in March-April and one in December. 41 Different factors might have contributed to an indirect pandemicrelated increased mortality over time of the pandemic period, and eventually yielded the maximum number of excess deaths estimated in 2022. Nevertheless, the persistence of excess mortality in 2023, and the burden on men under 60 years old remains unexplained and raises important concerns.

In 2020 and 2021, direct COVID-19 mortality was above excess mortality. The virus killed not only people who would not have died in the absence of a pandemic (amount of excess deaths) but also people who would have died from other causes, resulting in a decrease in other causes of death in 2020 and 2021. 32 33 Unfortunately, causes of death are not yet available in France for the years 2022 and 2023, but the higher estimated number of excess deaths than that of COVID-19-attributed deaths likely reflects a long-term indirect impact of the pandemic, possibly increasing mortality related to modifications of patient management and healthcare system organisation. A similar pattern for the year 2022 was also reported in other countries, 42 43 suggesting a similar impact of the pandemic on healthcare systems and mortality not only in France. Further research is needed to better understand the various features contributing to this perturbation of mortality trends.

## **Strengths and limitations**

This study is the first to date to provide a complete and detailed toll of the COVID-19 pandemic on mortality in France from 2020 to 2023. A major strength of the study is the exhaustivity and the accuracy of the toll, precisely estimated by taking into account major parameters influencing mortality such as age-specific and sex-specific evolution over time and changes in population structure. As a nationwide cohort study, the present study is fully exhaustive for France, and the method used can be extended to other countries, provided comparable data details on mortality and population structure.

Some limitations must nevertheless be noted. The study predictions are based on the assumption that in the absence of the COVID-19 pandemic, expected



mortality in the corresponding years would have followed the trends that were observed for the previous 10 years (including potential specific patterns for each age and sex) and this cannot be ascertained.

Estimates of YLL were calculated by applying the life expectancy of each person in excess mortality without considering underlying health conditions. The health status of the deceased was not documented at all in the database, but on average, their health condition was likely poorer than the average of the same-age and same-sex population, with a resulting lower life expectancy. Indeed, many studies reported that deaths from COVID-19 were positively associated with the presence of comorbidities  $^{44}$   $^{45}$  and the total number of YLL was found to be 12% lower than expected in Hungary when comorbidities were taken into account. 18 In a previous study, Quast et al decided to reduce the expected life expectancy by 25% to take this point into account. 46 The present study did not adopt any correction, so the reader must be cautious when interpreting the numeric YLL presented here, which may be overestimated. Nevertheless, the main study result on this topic concerns the increasing trend of progression over time, and at least the shape of this trend remains fully reliable. Estimates of the number of deaths officially attributed to COVID-19 should also be treated with caution. Indeed, some crucial parameters, such as the availability of tests and coding practices, varied greatly over the course of the pandemic, making strict interpretation of the official count uncertain. However, even if they are potentially underestimated, the 43 882 COVID-19 attributed deaths in 2022 and 2023<sup>34</sup> are far from explaining the 70484 excess deaths estimated for these 2 years.

#### **CONCLUSION AND PERSPECTIVES**

This study provides the first comprehensive analysis of the impact of the pandemic on mortality in France between 2020 and 2023. Despite a fall in excess mortality in 2021 and 2023, the number of YLL remains at a critical level, reflecting substantial losses among individuals under 60 years old, particularly men. This 4-year period of unprecedented excess mortality highly suggests a lasting indirect impact of the COVID-19 pandemic on the health-care system, even in 2023. Further research is essential to understand the reported trends and mitigate future risks.

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**Contributors** GH and NL initiated and supervised the study. All authors designed the experimental plan. PM managed data and performed the analyses. All authors take responsibility for the integrity of the data and the accuracy of the data analysis. PM is the guarantor and prepared the first draft of the manuscript. All authors contributed to interpretation of the data, critically revised the manuscript, and approved the final version.

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