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Centenarian Mortality Rate During COVID-19: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Marked by high mortality rates on a global scale, with disease mortality being notably focused among older adults, the COVID-19 pandemic has become a significant health crisis. Despite the numerous publications on COVID-19 mortality among older adults, there is still a gap in knowledge when considering centenarians, as there is no systematic review and meta-analysis that summarizes COVID-19 mortality in centenarians globally.

Objective: This study aims systematically review and synthesize global evidence on COVID-19 mortality rates among centenarians and the population of older adults worldwide, whether residing in long-term health facilities, hospitals, or their homes.

Methods: An automated search was conducted on the following databases: PubMed, Scopus, and Web of Science. Observational studies, both cohort and case-control, were selected. Quality assessment of the selected studies was based on the Joanna Briggs Institute critical appraisal tool for observational cohort and case-control studies. Three independent authors conducted the searches, and any possible disagreements were resolved by consensus. A meta-analysis of mortality proportions will be conducted to calculate the raw, logit, and arcsine proportions for all studies included in our meta-analyses. Heterogeneity between studies with a significance of P=.05 will be assessed by calculating the I2 value using the DerSimonian and Laird method for random effects. Odds ratios and 95% CIs for dichotomous data and weighted mean risk differences and 95% CIs for continuous variables will be calculated. Further subgroup analyses will be attempted to explore heterogeneity among over 6.7 million older adults. Leave-one-out sensitivity tests will be conducted to assess the robustness of our results. The meta-analysis will be conducted using R software version 4.4.2 (R Foundation for Statistical Computing).

Results: A total of 4 studies were included in our systematic review and meta-analysis. Of the included studies, 3 are retrospective cohort studies and 1 is an observational retrospective case-control study. As for study group size, 1 cohort study was conducted on a population of less than 1000 participants, 2 studies (1 cohort and 1 case-control) involved more than 10,000 participants, and 1 cohort study included more than 6 million participants. Using multiple estimators (raw-, logit-, and arcsine-transformed proportions; risk differences; and odds ratios) to quantify differential outcomes, centenarian patients diagnosed with COVID-19 during the period from December 2019 to December 2024 compared to other older adults their rate of mortality due to COVID-19 illness and not due to other or combined variables was found insignificant.

Conclusion: This meta-analysis provides the first comprehensive synthesis of COVID-19 mortality in centenarians, demonstrating that while rates are elevated, the difference from other older adults is modest and often not statistically significant.

Keywords: Coronavirus; Pandemic; Mortality; Covid-19; Elderly; Centenarians; Systematic Review; Meta-Analysis.

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Introduction

Novel coronavirus cases were first detected in China in December 2019, with the virus spreading rapidly to other countries worldwide. This led WHO to declare a Public Health Emergency of International Concern (PHEIC) on 30 January 2020 and to mark the outbreak as a pandemic on 11 March 2020 [1,2]. The aim of this study is to conduct a systematic review and meta-analysis of studies published between December 2019 and December 2024 on the rate of COVID-19 mortality in centenarians (ie, individuals aged 100 years and older) versus older adults aged 60-99 years (hereafter referred to simply as other older adults) [3]. Since the beginning of the pandemic, more than 777 million people have contracted the severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) globally, and a total of over 7.1 million people have lost their lives due to COVID-19 until now [4]. Mortality of COVID-19 increases with age while children were observed less susceptible to death [5,6]. Italy was the first European country to be affected by COVID-19 [7]. The biggest cluster of cases occurred in Lombardy, the most populous Italian region, and older people were hit in the hardest way [8]. In this population, Marcon et al [8] questioned if the COVID-19 mortality in was lower than that in other older adults and whether sex differences exist in mortality among different age classes.

Comparisons were made using total mortality (i.e., not only confirmed COVID-19 cases) at the peak of infection (March 2020) against March's total mortality of previous years. They did not find reduced mortality in centenarians relative to non-centenarians but highlighted a difference between sexes across different age classes. While mortality in those aged 60-99 years was much higher in men than in women, the rate at which the risk increased by age was slower in men than in women, the rate at which the risk increased by age was slower in men than in women, such that centenarian women had a higher mortality rate. They suggested that the pro-inflammatory status of older adults, referred to as inflammageing, could explain such age-related vulnerability. Despite the observations of multiple studies measuring the mortality rate in older adults, studies concerning mortality in centenarian patients with COVID-19 remain very scarce [9,10]. Addressing this gap is essential to reinforce our understanding of the unique challenges faced by the centenarians and enable more effective health planning. This, in turn, facilitates the development of targeted treatment approaches with proper interventions tailored to the specific health needs of this demographic, particularly in situations of health crises like the COVID-19 pandemic [11,12,13]. In view of the foregoing, the aim of this study is to investigate the mortality rates in centenarians worldwide due to COVID-19.

Materials and Methods

The protocol for our systematic review and meta-analysis was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [14]. Our meta-analysis study will be conducted in compliance with the guidelines detailed in the Cochrane handbook for systematic reviews of interventions [15].

Inclusion and Exclusion Criteria

PICOS (population, intervention, comparison, outcomes, and study) design for eligibility criteria [16] was adopted in this study (Figure 1). The population of interest will be individuals aged 100 years and older. The intervention will be testing positive for COVID-19. The comparison group will be individuals aged 60-99 years. The outcome of interest will be mortality rates in both populations from COVID-19. The studies included will comprise only peer-reviewed, longitudinal observational cohort and case-control studies published from December 2019 until December 2024 in English.

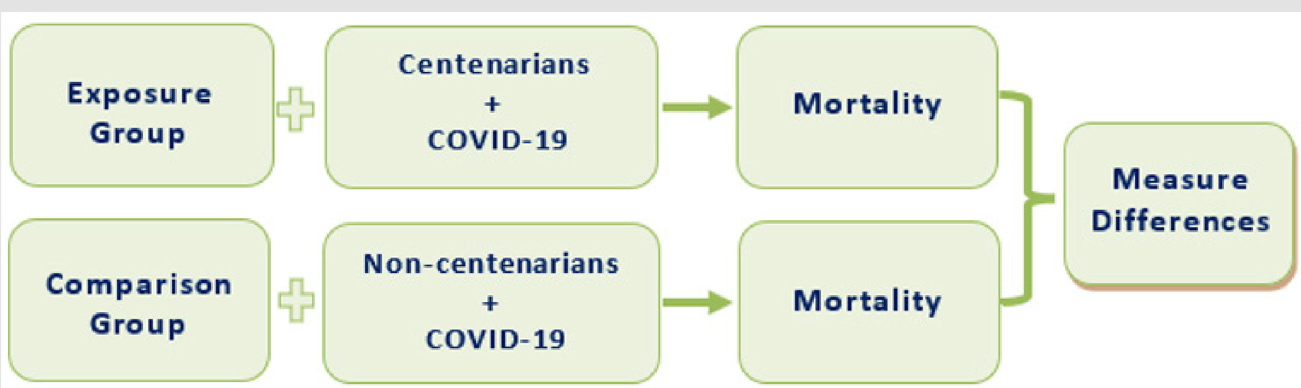

Figure 1: PICOS (population, intervention, comparison, outcomes and study) design for eligibility criteria.

Exclusion Criteria

The exclusion criteria for this meta-analysis were:

(a) Population: studies with no centenarian participants

(b) Intervention: mortality studies during COVID-19 pandemic but deaths not due to COVID-19

(c) Comparison group: individuals less than 100 years not included in the study

(d) Outcome: studies that do not present mortality rate as their effect measure

(e) Studies: those which do not fit or answer our research question.

Systematic reviews, scoping reviews, book records and research papers not available in English language will also be excluded. The restriction regarding publication time (Dec 2019–Dec 2024) is for the temporality of the COVID-19 pandemic but at the same time to widen our search window to include studies that were published after the pandemic was declared over in May 2023 [17].

Information Sources, Search Strategy, and Study Selection

PubMed, Scopus, and Web of Science electronic search databases were consulted by 2 researchers on January 7, 2025, to search for studies published between December 2019 and December 2024 to identify any cohort and case-control studies that investigated the relationship between COVID-19 diagnosis and mortality in centenarians versus other older adults. The main keywords used were "centenarians" and "covid" in addition to their variations (Table 1). In the search strategy, keywords were systematically combined using the Boolean operators "AND" and "OR" to refine and expand the retrieval of relevant literature. The references of the studies included in the full-text evaluation phase were reviewed independently by the 2 researchers to identify potentially relevant studies that were not considered in earlier search phases. The studies were screened against the eligibility criteria in 2 phases: title and abstract screening followed by full-text screening. In cases of disagreement between the 2 reviewers at any stage, a consensus process was undertaken. If a resolution was not reached, a third reviewer was consulted for resolution. If data are missing or unclear, attempts will be made to contact the study authors for clarification. If contact cannot be established, the study will be excluded from our analysis, and this will be addressed in the discussion section. Science reviews, systematic reviews, and meta-analyses found in the automated search were excluded from our study.

Table 1: Search Strategy.

Database	Query	Number of Studies
PubMed	("centenarians"[MeSH Terms] OR "centenarians"[All Fields] OR "centenarian"[All Fields]) AND ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "covid"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19"[All Fields])	34
Scopus	(TITLE-ABS-KEY (centenarian AND covid)) OR (TITLE-ABS-KEY (*supercentenarian* OR semi*super-centenarian) AND ORIG-LOAD-DATE AFT 20240314) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "no") OR LIMIT-TO (DOCTYPE , "cp") OR LIMIT-TO (DOCTYPE , "sh") OR LIMIT-TO (DOCTYPE , "le") OR LIMIT-TO (DOCTYPE , "ed"))	29
Web of Science	(ALL=(centenarian)) AND ALL=(covid)	38

Data extracted from the selected studies included

(1) Author and year of publication

(2) Name of the journal

(3) Study design

(4) Country of origin of the study

(5) Study objective

(6) Sample size

(7) Period of data collection

(8) Statistical test used

(9) Age of participants

(10) Sociodemographic details (i.e., living alone or in a long term health facility)

(11) COVID-19 status, (i.e., positive or negative), and

(12) Measured outcome.

A spreadsheet in Microsoft Excel was used to record the necessary data for running the meta-analysis. Data analyses were presented in tables and charts, and their interpretation will be discussed.

Risk of Bias and Study Quality Assessment

Funnel plots were constructed to visually assess publication bias in our meta-analysis [18]. They were structured as scatter plots, with study effect sizes on the x-axis and a measure of study precision (standard error) on the y-axis. Because visual inspection can be subjective, statistical Egger regression tests supplemented visual assessment for more robust conclusions. In addition, trim-and-fill analysis [19] were considered to assess publication bias and display the heterogeneity of the studies included in the systematic review. The Joanna Briggs Institute critical appraisal tool was used to evaluate the quality of observational cohort and case-control studies [20]. The quality assessment for the selected literature was evaluated independently by all authors (Supplementary Material)

Synthesis of Results

Our preliminary search in the 3 databases resulted in a total of 101 research papers. An additional paper was found in Google scholar, totalling 102 papers. A third researcher was consulted for help with screening the 102 articles, reviewing their respective abstracts and removing duplicates. This resulted in 54 articles remaining. The 54 articles were downloaded and fully reviewed to check their eligibility for our study. Data was extracted from the chosen studies into tables and charts, and their interpretation is discussed. Overall mortality proportions were compared among studies to calculate pooled raw, logit, and arcsine proportions for all studies included in our meta-analysis. A random effects model for meta-analyses will be calculated using the DerSimonian and Laird method. This model acknowledges that studies included in the analysis may have different underlying effect sizes, rather than assuming a single true effect size across all studies, as in the fixed-effect model [21]. This means that, in addition to the within-study variability, there is also between-study heterogeneity that needs to be accounted for. The random effects model estimates both the within-study (I2) and between-study (τ^2) variances. Heterogeneity will be evaluated with a significance level of P=.05. An assessment of heterogeneity with I2 values will be presented. Heterogeneity of around 25% will be considered low, around 50% moderate, and around 75% high.

The arcsine transformation of proportions will be primarily considered in our meta-analyses because it stabilizes the variance of proportion data, especially when proportions are close to 0 or 1 (ie, when studies report very low or very high proportions and variance instability is most pronounced) [22]. Arcsine transformation makes the data more suitable for standard meta-analytic analysis techniques that assume normality and homogeneity of variance. Weighted mean risk differences and 95% CIs will be calculated for continuous variables. Odds ratios and 95% CIs for each dichotomous data outcome will also be determined [23]. Individual study results will be visually summarized using forest plots to display both individual study estimates and the pooled estimate from the meta-analysis [15]. Meta-analyses were conducted using R software version 4.2.2 (R Foundation for Statistical Computing).

Subgroup Analysis and Sensitivity Test

Further subgroup analyses will be conducted considering other factors such as country, age brackets, and long-term care facility versus community dwelling to explore the heterogeneity among the 6.7 million older adults included in our study [24]. This is to help explain whether there is a variation in effect sizes across studies. Leave-one-out sensitivity tests will illustrate how far the calculated pooled effect estimate shifts when each study is excluded one at a time and recalculating the pooled effect size [25]. This will help identify whether any single study disproportionately influences our overall findings and ensure that our conclusions are not unduly influenced by any single study, thereby enhancing the credibility of our synthesized evidence.

Ethical Considerations

Ethical approval is not required for this protocol as it is a systematic review that includes secondary data from published studies. In this study, participants are not actively recruited, and data are not collected directly from them. The findings of the systematic review and meta-analysis will be disseminated through peer-reviewed publications.

Results

A total of 19 qualitative and 4 quantitative studies were found relevant and were considered in our systematic review and meta-analysis (Figure 2). The qualitative studies were particularly valuable in guiding the methodology of our meta-analysis, informing our interpretation of the results, and shaping our conclusions. Additionally, they played a crucial role in constructing the literature review and establishing the background for our hypothesis by highlighting existing gaps in the literature. Of the 4 included quantitative studies, 3 are retrospective cohort studies and 1 is an observational, retrospective, case-control study. As for study group size, 1 cohort study was conducted on a population of less than 1000 participants [26], 2 studies (1 cohort [27] and 1 case-control [28]) involved more than 10,000 participants, and 1 cohort study included more than 6 million participants [29].

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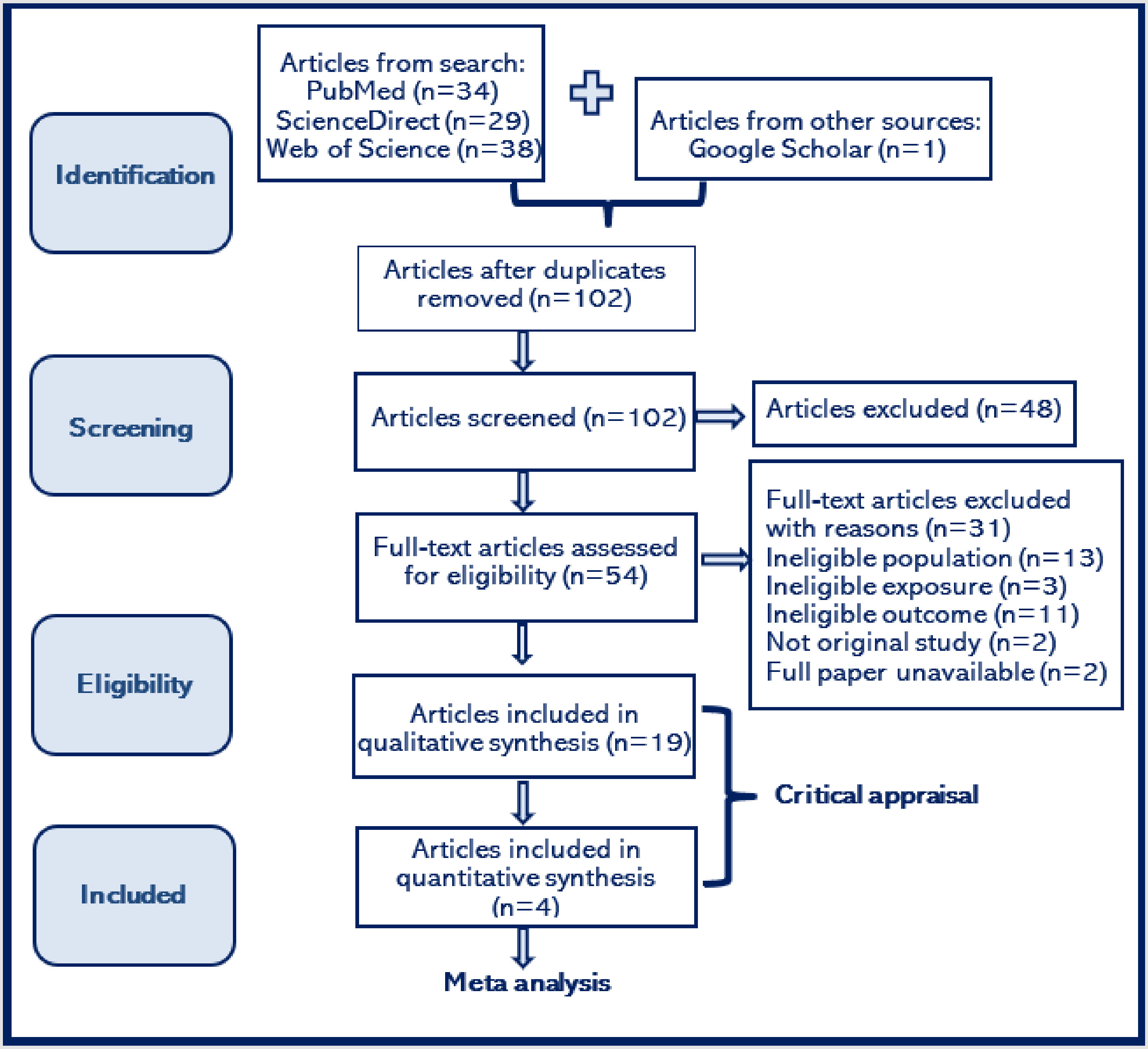

Figure 2: PRISMA (Preferred Reporting Items for Systematic review and Meta-Analyses) Flowchart.

Exposure and Outcome Categorization

The primary exposure for the meta-analyses was COVID-19 diagnosis. Studies included various settling of centenarians, whether in their home or in a long-term care facility. The included studies collected and kept health record data for every participant. The primary outcome for our study was mortality, all COVID-19 cases included in the studies were considered in our meta-analyses.

Quality and Risk of Bias Assessments

The quality for the selected literature was evaluated independently by all reviewers in this study according to the Joanna Briggs Institute (JBI). The JBI Critical Appraisal Checklist for case-control, and cohort studies was used to check the quality of studies and assess the risk of bias. Any differences between reviewers' evaluation were settled by discussion and consensus.

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Qualitative Synthesis and Quantitative Statistical Analysis

Reviewers organized and recorded the details of each study, including study design, country/region, date of COVID-19 diagnosis and recovery or death, study population and health records data sources. The odds ratio (OR) for the incidence of mortality in exposed vs non-exposed were calculated and reported based on raw data documented in the included studies. DerSimonian-Laird random-effects model was used to pool risk estimates across studies [30], reported as odds ratios (ORs) with 95% confidence intervals (95% CIs). Additionally, the weighted mean risk difference (RD) with 95% CI was computed to evaluate mortality rate differences between case and control groups. Heterogeneity among studies was also assessed. A regression analysis was performed to assess potential bias or influence of study design (prospective cohort vs. case-control) on the effect estimates [31].

Results and Discussion

Data was extracted from the chosen studies into tables and charts. Overall mortality proportions were compared among studies to calculate pooled raw, logit, and arcsine proportions for all studies included in our meta-analysis. A random effects model for meta-analyses was calculated using the DerSimonian and Laird method. This model acknowledges that studies included in the analysis may have different underlying effect sizes, rather than assuming a single true effect size across all studies, as in the fixed-effect model. This means that, in addition to the within-study variability, there is also between-study heterogeneity that needs to be accounted for. The random effects model estimates both the within-study (I2) and between-study (τ^2) variances. Heterogeneity was evaluated with a significance level of P=0.05. An assessment of heterogeneity with I2 values was presented. Heterogeneity of around 25% will be considered low, around 50% moderate, and around 75% high. The arcsine transformation of proportions was primarily considered in our meta-analyses because it stabilizes the variance of proportion data, especially when proportions are close to 0 or 1 (ie, when studies report very low or very high proportions and variance instability is most pronounced). Arcsine transformation makes the data more suitable for standard meta-analytic analysis techniques that assume normality and homogeneity of variance. Weighted mean risk differences and 95% CIs was calculated for continuous variables. Odds ratios and 95% CIs for each dichotomous data outcome was also determined. Individual study results were visually summarized using forest plots to display both individual study estimates and the pooled estimate from the meta-analysis [15]. Meta-analyses will be conducted using R software version 4.2.2 (R Foundation for Statistical Computing).

Subgroup Analysis and Sensitivity Test

Further subgroup analyses will be conducted considering other factors such as country, age brackets, and long-term care facility versus community dwelling to explore the heterogeneity among the 6.7 million older adults included in our study. This is to help explain whether there is a variation in effect sizes across studies. Leave-one-out sensitivity tests will illustrate how far the calculated pooled effect estimate shifts when each study is excluded one at a time and recalculating the pooled effect size. This will help identify whether any single study disproportionately influences our overall findings and ensure that our conclusions are not unduly influenced by any single study, thereby enhancing the credibility of our synthesized evidence.

Qualitative Synthesis of Included Studies

Details of the included studies are summarized in Table 2. Of the 4 included studies, 3 are case-control studies [26,27,29] and 1 retrospective cohort study [28]. Of the included studies, 3 were from European countries [26,27,29], and 1 from Columbia [28]. All studies included centenarian and non-centenarian patients. All studies identified mortality from COVID-19 as their primary outcome. Effect estimates were calculated from the raw data retrieved from each included study. A meta-analysis was performed by pooling effect estimates from the subgroups, centenarians and non-centenarians, respectively.

- **Odds Ratio (OR):** is a consistent measure of the effect of an exposure, was used for comparing the odds of precipitating an incidence between the exposed vs the non-exposed in the compiled dataset.
- **Risk Difference (RD):** was used to present the difference in mortality rates for each group in the dataset, centenarian vs. non-centenarian.

Table 2: Details of Studies Meeting Inclusion Criteria.

Author, Pub Yr	Study	Region	Centenarian (Case)			Non-Centenarian (Control)		
			Case	Case Death	Mortality %	Control	Control Death	Mortality %
Couderc, et al. [26]	Retro-spective, cohort	15 nursing homes in Marseille, France	12	6	50.00	309	66	21.36
Gallert, et al. [27]	Retro-spective, cohort	LTCF, Germany	8264	40	0.48	403725	5,493	1.36
Claudia, et al. [28]	Population based, cohort	Columbia	1,005	373	37.11	6,312,867	3,508,691	55.58
Cruces, et al. [29]	Population based, case-control	Basques country, Spain	325	95	29.23	21,170	4,977	23.51

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Quantitative Analysis

A total of 6,747,677 individuals were included for this meta-analysis, including 9,606 centenarians and 6,738,071 non-centenarians. Across all 4 studies, 3,519,741 mortalities were recorded, 514 of which were centenarians.

Raw, Logit and Arcsine Proportions

The raw and arcsine proportion analyses, but not logit proportion, showed that the mortality rate in centenarians diagnosed with COVID-19 is significant. We further analysed the data to get the combined odds ratio (OR) and risk difference (RD) for all studies, to determine whether a significant relation exists.

Odds Ratio (Or)

The pooled odds ratio (OR = 0.81, 95% CI: 0.47 to 1.38, p = 0.43) suggests a possible protective effect of COVID-19 in centenarians by 19 %, but this result is not statistically significant because the confidence interval includes 1 and the p-value is 0.43. statistical weight of each study; 95% CIs are indicated by the error bars; and overall OR with 95% CI for all studies is depicted as a diamond. An OR less than 1 suggests a protective effect (i.e., the exposure reduces the odds of the outcome). In this case, the pooled OR is 0.81, which suggests reducing the odds of the outcome by approximately 19%. However, since the CI includes 1 and p-value is 0.43, this confirms that the association is not statistically significant.

Risk Difference (Rd)

Risk difference is the probability of an outcome between two groups. It is calculated as the difference between the proportion of events in the exposed group and the proportion in the unexposed group. The estimated average effect suggests 1% lower risk or protective effect of the outcome in the exposed group compared to the control group. This implies almost no difference in risk between groups. The true RD could range from 7% lower risk (0.93) to 5% higher risk (1.05); however, this effect is not statistically significant, no evidence for harm or benefit.

Publication Bias and Heterogeneity

The method we used to account for heterogeneity among studies is the DerSimonian and Laird method (DL) as it analyses two sources of variability: variability within each study and variability among all studies. Heterogeneity Metrics: I2 index measures the percentage of variability in exposure effect estimates, τ^2 measures between-study variance; higher values mean higher variability while Cochran's Q test confirms heterogeneity when p-value is <0.05.

Centenarian Mortality Rate

The pooled mortality proportion is 0.24, (95% CI: 0.01 to 0.62) in centenarians. Across all studies, an estimated 24% of centenarians diagnosed with COVID-19 experienced mortality, the true proportion falls between 1% and 62%—a wide but statistically significant range, p=0.01. Heterogeneity Metrics: (I^2 = 99.80%, τ^2 = 0.16, p < 0.0001). I2 index measures the percentage of variability in exposure effect estimates. In other words, 99.80% of the effect estimate, mortality, is due to between study differences rather than chance. τ^2 measures between-study variance; higher values mean more variability while Cochran's Q test confirms significant heterogeneity (p < 0.001), (Figures 3,4).

```
Random-Effects Model (k = 4; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.1561 (SE = 0.1832)
tau (square root of estimated tau^2 value):      0.3951
I^2 (total heterogeneity / total variability):   99.80%
H^2 (total variability / sampling variability):  496.33

Test for Heterogeneity:
Q(df = 3) = 1488.9880, p-val < .0001

Model Results:

estimate      se     zval     pval    ci.lb    ci.ub
  0.5122  0.2007   2.5523   0.0107   0.1189   0.9055  *

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

> transf.iarcsin(0.5122)
[1] 0.2401942
> transf.iarcsin(0.1189)
[1] 0.01407072
> transf.iarcsin(0.9055)
[1] 0.6189502
```

Figure 3: DerSimonian-Laird RE Model for Centenarians.

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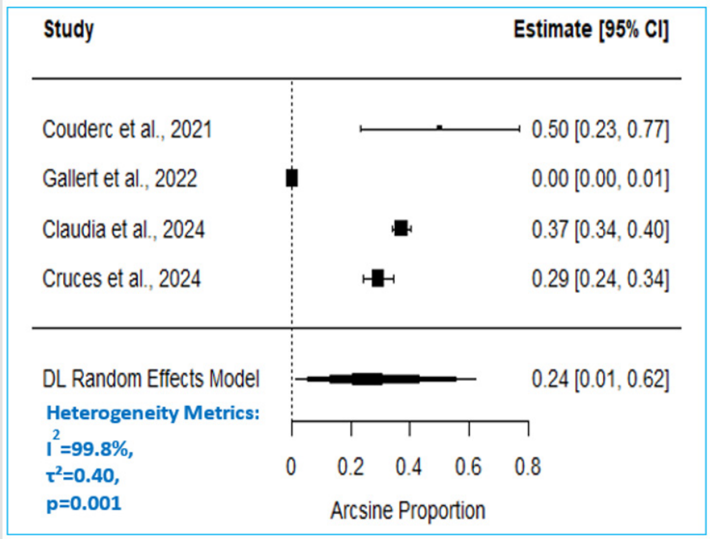
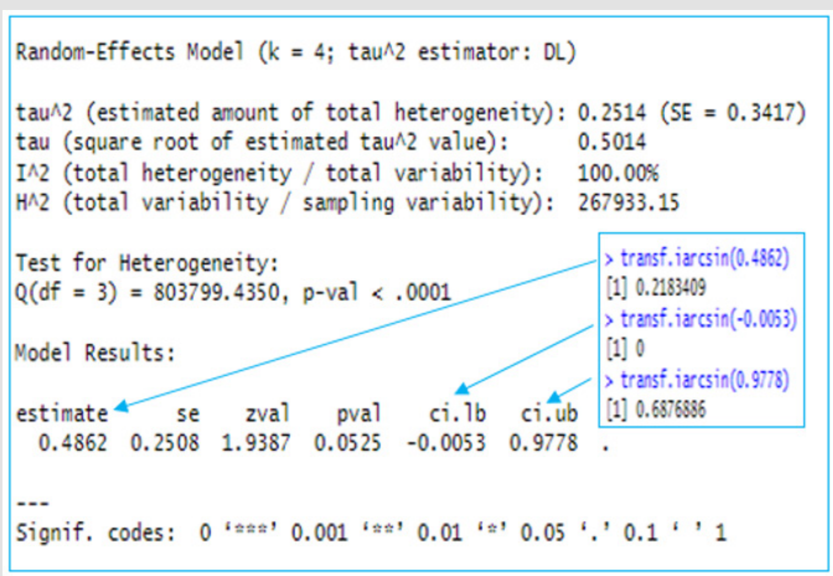


Figure 4: Forest plot showing mortality proportion in Centenarians.

Non-Centenarians Mortality Rate

The pooled mortality proportion in the non-centenarian group is 0.22, (95% CI: 0 to 0.69). Across all studies, an estimated 22% of non-centenarians diagnosed with COVID-19 experienced mortality, which is a little less than the proportion for centenarians (24%). The non-centenarian event proportion likely falls between 0% and 69%—a wide but statistically significant range (p=0.05). Heterogeneity Metrics: (I^2 = 100.00%, τ^2 = 0.25, p < 0.0001). The percentage of variability in exposure effect estimates is 100%. In other words, 100% of the effect estimate, mortality, is due to between study differences and not chance. τ^2 measures moderate variance while Cochran's Q test confirms significant heterogeneity (p < 0.001), (Figures 5,6). We used arcsine proportions when running our pooled estimate analyses because arcsine stabilises variance for extreme proportions (near 0% or 100%), handles sparse data better than raw proportions and reduces bias when event rates vary widely across studies. Contrast with OR/RD: may have been insignificant due to rare events or imbalanced group sizes, while arcsine accounts for these issues.



```
Random-Effects Model (k = 4; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.2514 (SE = 0.3417)
tau (square root of estimated tau^2 value):      0.5014
I^2 (total heterogeneity / total variability):   100.00%
H^2 (total variability / sampling variability):  267933.15

Test for Heterogeneity:
Q(df = 3) = 803799.4350, p-val < .0001

Model Results:

estimate      se    zval    pval    ci.lb   ci.ub
  0.4862  0.2508  1.9387  0.0525  -0.0053  0.9778  .

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
> transf.iarcsin(0.4862)
[1] 0.2183409
> transf.iarcsin(-0.0053)
[1] 0
> transf.iarcsin(0.9778)
[1] 0.6876886
```

Figure 5: DerSimonian-Laird RE Model for Non-Centenarians.

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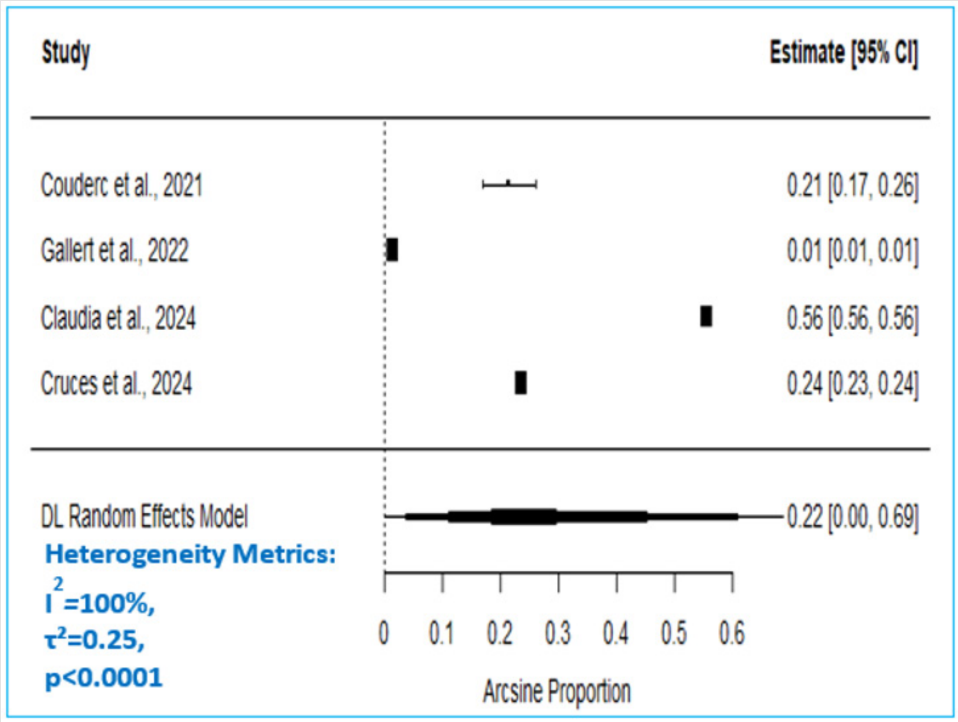

Figure 6: Forest plot showing mortality proportion in Non-Centenarians.

Leave-One-Out Sensitivity Analyses

The leave-one-out sensitivity analysis plot illustrates how the pooled effect estimates from our meta-analysis shifts when each study is excluded one at a time. In Figure 7, the blue line represents the recalculated pooled estimate for each scenario, with each point corresponding to the omission of a specific study indicated on the x-axis. This visualizes the impact of each individual study on the overall meta-analytic result. The red dashed line displays the original pooled estimate (log odds ratio) calculated with all studies included. The x-axis lists the omitted studies, while the y-axis shows the pooled effect size (log odds ratio) for each leave-one-out analysis.

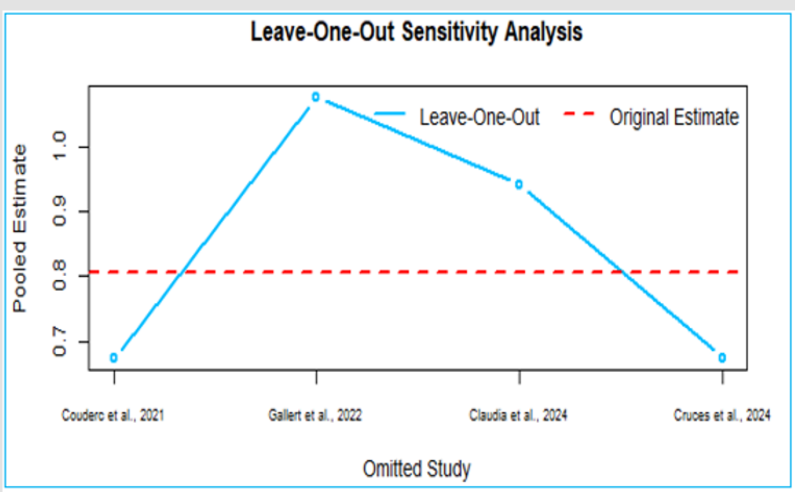

Figure 7: Leave-One-Out Sensitivity Analysis.

Key Findings from the Plot

The leave-one-out analysis shows that, although the pooled estimates (blue line) fluctuate slightly with the omission of each study, they consistently remain close to the original pooled estimate (red dashed line). Omitting any individual study does not result in a substantial change to the overall effect size, and even the largest deviations are minor. This suggests that no single study exerts a disproportionate influence on the meta-analysis results. Consequently, our findings are robust and stable, reinforcing the reliability and credibility of the overall conclusions.

Leave-One-Out Forest Plot

Figure 8 forest plot presents the leave-one-out sensitivity analysis for the meta-analysis of COVID-19 mortality in centenarians. Each row shows the meta-analysis results recalculated after omitting one study. The black square represents the pooled odds ratio (OR) estimate when that study is omitted; the horizontal line is the 95% confidence interval (CI). The vertical black dashed line represents the original pooled OR with all studies included. The vertical red dotted line at OR=1 means null effect (no difference). The columns on right side show: The p-value: or the statistical significance of the pooled effect after omitting the study, tau^2: Between-study variance (heterogeneity) after study omission, I^2: Percentage of variability due to heterogeneity, not chance, Q: Cochran's Q statistic for heterogeneity. Estimate [95% CI]: The pooled odds ratio and its 95% CI for each leave-one-out scenario.

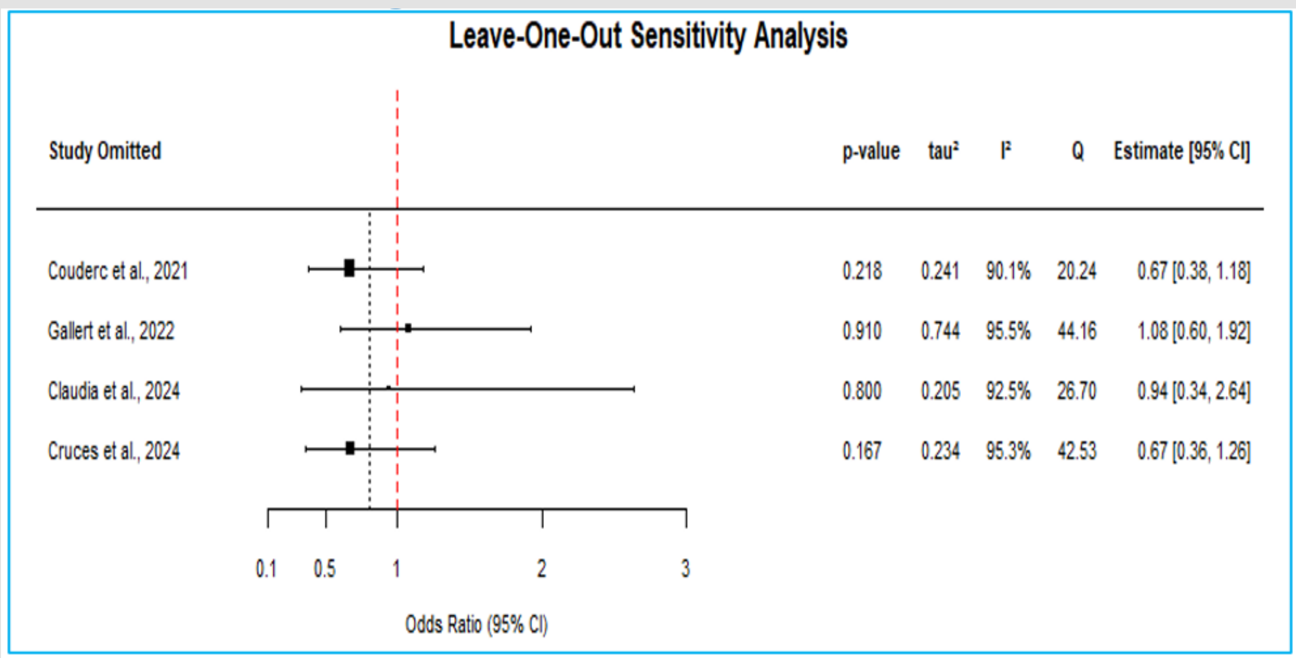

Figure 8: Leave-One-Out Forest Plot.

Interpretation

- **Robustness:** The pooled OR remains close to the original estimate (red dashed line) regardless of which study is omitted. All 95% CIs overlap substantially, and none of the leave-one-out results are statistically significant (all p-values > 0.05).
- **Heterogeneity:** I^2 values remain high (>90%) in all scenarios, indicating substantial heterogeneity among studies even when any single study is omitted. Tau^2 and Q also remain high, reinforcing this.
- **Influence:** No single study, when omitted, causes a dramatic shift in the pooled effect size or its statistical significance. For example, omitting Gallert et al., 2022, increases the pooled OR to 1.08, but the CI is wide (0.60, 1.92) and still not significant. Omitting other studies yields similar patterns.
- **Overall:** No study unduly influences the overall meta-analytic result. Findings are robust, the pooled effect estimate, and its interpretation do not depend heavily on any single study. Heterogeneity remains high regardless of which study is omitted, suggesting variability is not driven by a single outlier. Our meta-analysis results are stable and credible; the exclusion of any one study does not significantly alter the pooled odds ratio or the overall interpretation.

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Centenarian Subgroup Risk Analyses

The following subgroup analyses were conducted:

- Odds Ratio for LTCF
- Risk Difference for LCTF
- Odds Ratio for Community Dwelling
- Risk Difference for Community Dwelling
- Odds Ratio in Developed Countries
- Risk Difference in Developed Countries

Odds ratio and risk difference for developing countries was not possible because we only had one study, Claudia, et al. [28], conducted in developing countries and no further studies to compare.

Odds Ratio for LTCF

The estimated average effect suggests 14% lower odds (since OR < 1) of the mortality outcome in the centenarian group compared to the non-centenarian group. The true OR ranges from 0.14 lower odds to 5.4 higher odds, however, this effect is insignificant, p>0.05, Figure 9, Table 3. The estimated OR effect suggests 14% lower odds (since OR < 1) of the outcome in the exposed group compared to the control group, however, this effect is insignificant, p<0.05, Figure 10.

Table 3: DerSimonian-Laird RE Model for Non-Centenarians.

Arcsine Proportion	ci.lb	ci.ub	p-val
0.22	0	0.69	0.05

```
Random-Effects Model (k = 2; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 1.6280 (SE = 2.5100)
tau (square root of estimated tau^2 value):      1.2759
I^2 (total heterogeneity / total variability):   91.73%
H^2 (total variability / sampling variability):  12.09

Test for Heterogeneity:
Q(df = 1) = 12.0864, p-val = 0.0005

Model Results:

estimate      se     zval     pval    ci.lb   ci.ub
 -0.1560  0.9398  -0.1660  0.8682  -1.9980  1.6860

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Figure 9: The Random-Effect Model, DerSimonian-Laird Method.

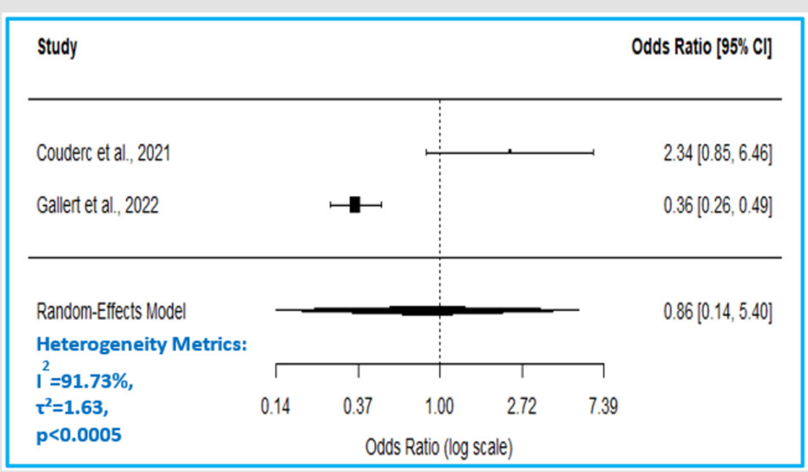

Figure 10: Odds Ratio Forest Plot for LTCF.

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Risk Difference for LCTF

The estimated average effect suggests 4% higher odds (since OR > 1) of mortality in the centenarian group compared to the control group. The true RD could range from 0.90 lower odds to 1.2 higher odds; however, this effect is insignificant, p>0.05, Figure 11, Table 4. The estimated average effect suggests 4% higher risk (since RD > 1) of the outcome in the exposed group compared to the control group, however, this effect is insignificant, p<0.05

Table 4: Pooled Odds Ratio for LTCF.

Pred	ci.lb	ci.ub	Pi.Ib	Pi.ub
0.86	0.14	5.4	0.04	19.1

Pooled RD	ci.lb	ci.ub	p-val
1.04	0.9	1.2	0.62

```
Random-Effects Model (k = 2; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.0074 (SE = 0.0195)
tau (square root of estimated tau^2 value):      0.0860
I^2 (total heterogeneity / total variability):   53.76%
H^2 (total variability / sampling variability):  2.16

Test for Heterogeneity:
Q(df = 1) = 2.1626, p-val = 0.1414

Model Results:

estimate      se    zval    pval    ci.lb   ci.ub
  0.0360  0.0736  0.4894  0.6246  -0.1082  0.1802

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Figure 11: LTCF Pooled Risk Difference using the DerSimonian-Laird Method.

Odds Ratio for Community Dwelling Centenarians

The estimated average effect suggests 10% lower mortality odds (since OR < 1) in community dwelling centenarians compared to non-centenarians. The true OR could range from 0.49 lower odds to 1.66 higher odds, however, this effect is insignificant, p>0.05, Figure 12, Table 5 The estimated average effect suggests 10% lower mortality odds (since OR < 1) of the outcome in the exposed group compared to the control group, however, this effect is insignificant, as the CI crosses one, Figure 13.

Table 5: Pooled Risk Difference for LTCF.

Pred	ci.lb	ci.ub	Pi.Ib	Pi.ub
1.04	0.9	1.2	0.83	1.29

Pooled RD	ci.lb	ci.ub	p-val
1.04	0.9	1.2	0.62

 DOI: 10.26717/BJSTR.2025.63.009925

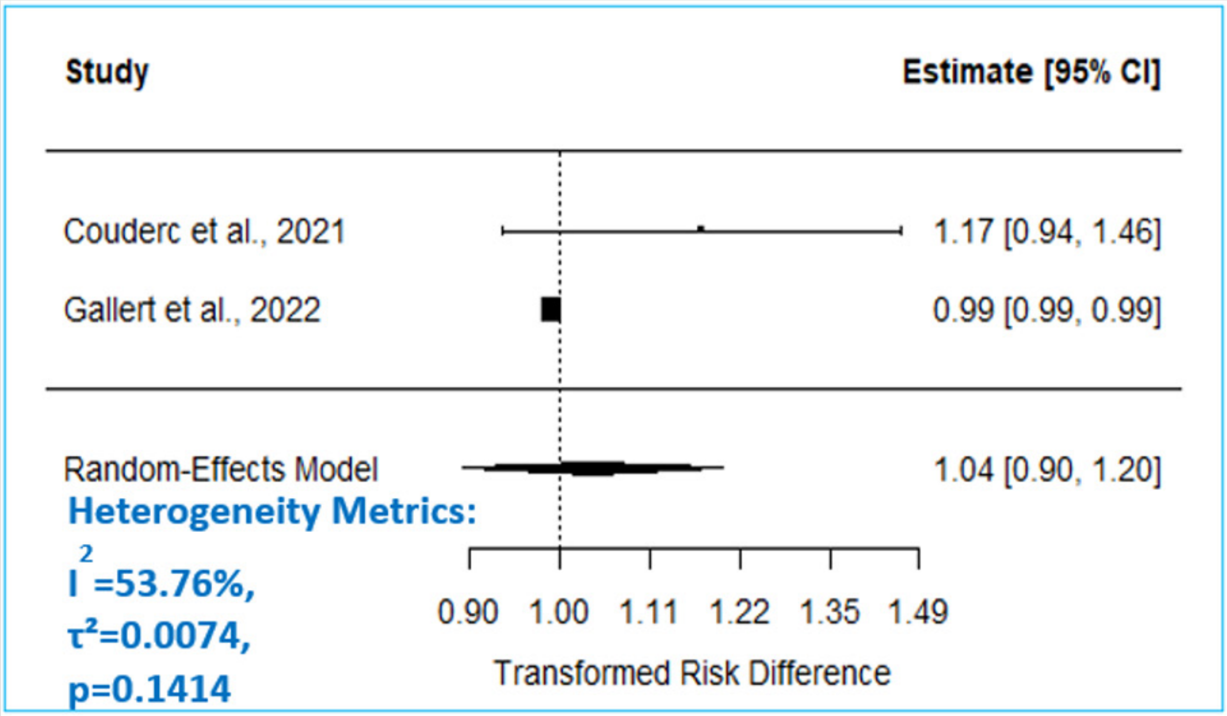

Figure 12: Risk Difference Forest Plot for LTCF.

```
Random-Effects Model (k = 2; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.1844 (SE = 0.2732)
tau (square root of estimated tau^2 value):      0.4295
I^2 (total heterogeneity / total variability):   95.46%
H^2 (total variability / sampling variability):  22.05

Test for Heterogeneity:
Q(df = 1) = 22.0461, p-val < .0001

Model Results:

estimate      se     zval    pval    ci.lb   ci.ub
 -0.1012  0.3107  -0.3257  0.7447  -0.7102  0.5078

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Figure 13: Community Dwelling Centenarians Pooled Mortality Odds Ratio.

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Mortality Risk Difference for Community Dwelling Centenarians

The estimated risk difference shows 3% lower mortality risk (since OR < 1) in community dwelling centenarians compared to non-centenarians. The true RD could range from 0.86 lower risk to 1.1 higher risk, however, this effect is insignificant, p>0.05, Figure 14, Table 6. The average RD suggests 3% lower mortality risk (since RD < 1) in the community dwelling centenarians group compared to non-centenarians, however, this effect is insignificant as the CI crosses one, Figure 15.

Table 6: Pooled Odds Ratio for Community Dwelling Centenarians.

Pred	ci.lb	ci.ub	Pi.Ib	Pi.ub
0.9	0.49	1.66	0.32	2.55

Pooled OR	ci.lb	ci.ub	p-val
90%	0.49	1.66	0.75

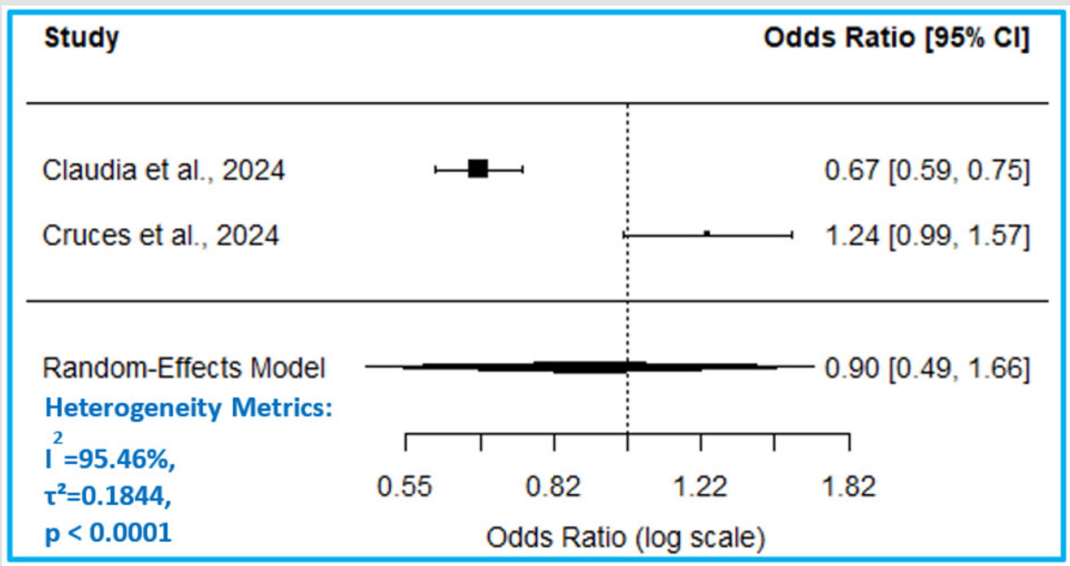

Figure 14: Odds Ratio Forest Plot for Community Dwelling Centenarians.

```
Random-Effects Model (k = 2; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.0072 (SE = 0.0106)
tau (square root of estimated tau^2 value):      0.0849
I^2 (total heterogeneity / total variability):   96.22%
H^2 (total variability / sampling variability):  26.48

Test for Heterogeneity:
Q(df = 1) = 26.4759, p-val < .0001

Model Results:

estimate      se     zval    pval    ci.lb   ci.ub
 -0.0265  0.0612  -0.4331  0.6650  -0.1464  0.0934

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Figure 15: Pooled Risk Difference for Community Dwelling Centenarians.

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Mortality Odds Ratio for Centenarians In Developed Countries

The estimated average effect suggests 6% lower mortality odds (since OR < 1) in centenarians compared to non-centenarians in developed countries. The true OR could range from 0.34 lower odds to 2.64 higher odds, however, this effect is insignificant, p>0.05, Figure 16, Table 7. The estimated average effect suggests 2% higher risk (since RD > 1) of the outcome in the exposed group compared to the control group, however, this effect is insignificant, as CI crosses one, Figure 16.

Table 7: Pooled Mortality Risk Difference for Community Dwelling.

Pred	ci.lb	ci.ub	Pi.Ib	Pi.ub
0.97	0.86	1.1	0.79	1.2

Pooled RD	ci.lb	ci.ub	p-val
97%	0.86	1.1	0.67

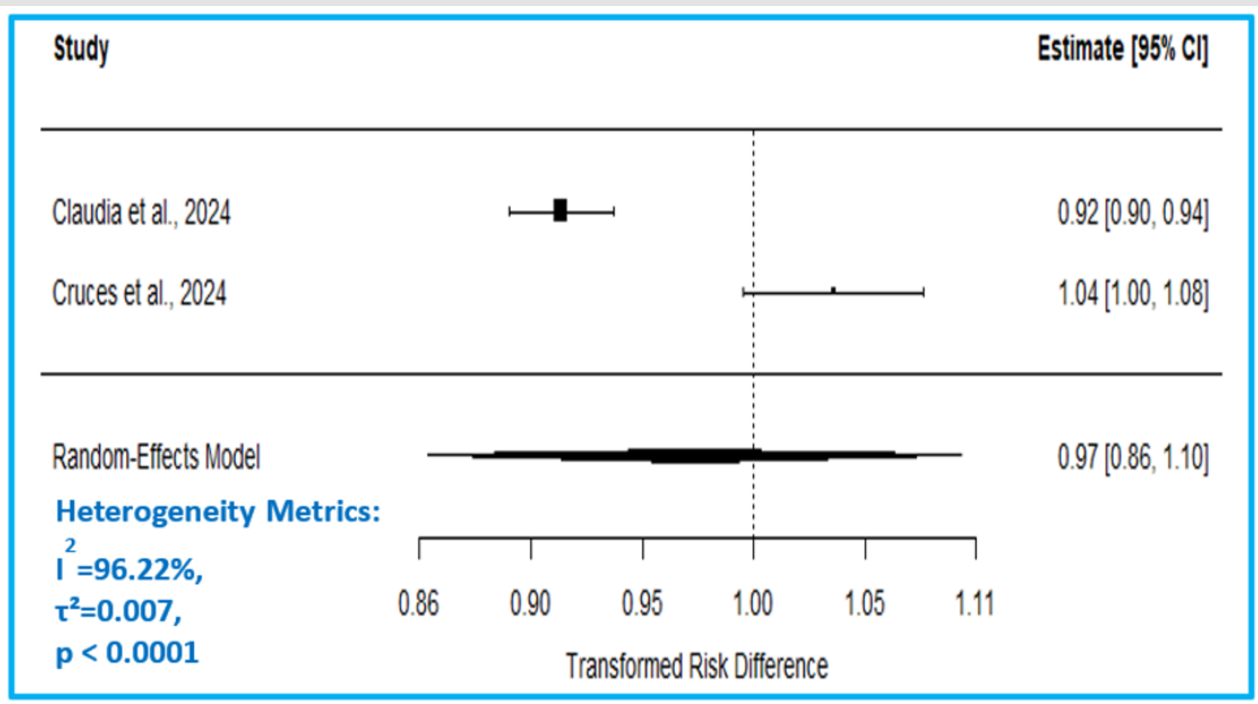

Figure 16: Mortality Risk Difference Forest Plot for Community Dwelling Centenarians.

Mortality Risk Difference for Centenarians in Developed Countries

The estimated average effect suggests 2% higher risk (since OR > 1) of the outcome in the exposed group compared to the control group. The true OR could plausibly range from 0.97 lower odds to 1.06 higher odds, however, this effect is insignificant, p>0.05, Figure 17, Tables 8-11. The estimated average effect suggests 2% higher risk (since RD > 1) of the outcome in the exposed group compared to the control group, however, this effect is insignificant as CI crosses one, Figures 18-22.

Table 8: Mortality Odds Ratio for Centenarians in Developed Countries.

Pred	ci.lb	ci.ub	Pi.Ib	Pi.ub
0.94	0.34	2.64	0.13	6.83

Pooled OR	ci.lb	ci.ub	p-val
94%	0.34	2.64	0.91

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Table 9: Comparison between Raw, Logit and Arcsine Proportions.

Centenarian Group

Raw Proportion	ci.lb	ci.ub	pval
0.28	0.03	0.53	0.03

Logit Proportion	ci.lb	ci.ub	pval
0.15	0.02	0.61	0.12

Arcsine Proportion	ci.lb	ci.ub	pval
0.24	0.01	0.62	0.01

Non-Centenarian Group

Raw Proportion	ci.lb	ci.ub	pval
0.25	-0.12	0.63	0.18

Logit Proportion	ci.lb	ci.ub	pval
0.16	0.02	0.7	0.19

Arcsine Proportion	ci.lb	ci.ub	pval
0.22	0	0.69	0.05

Note: Comparison: Raw, Logit and Arcsine proportions.

Table 10: Pooled Mortality OR across all Studies.

pred	ci.lb	ci.ub	pi.lb	pi.ub
0.81	0.47	1.38	0.26	2.47

Pooled OR	ci.lb	ci.ub	p-val
81%	0.47	1.38	0.43

Table 11: Pooled Mortality RD across all studies.

pred	ci.lb	ci.ub	pi.lb	pi.ub
0.99	0.93	1.05	0.88	1.11

Pooled RD	ci.lb	ci.ub	p-value
99%	0.93	1.05	0.69

```
Random-Effects Model (k = 3; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.7443 (SE = 0.9854)
tau (square root of estimated tau^2 value):      0.8627
I^2 (total heterogeneity / total variability):   95.47%
H^2 (total variability / sampling variability):  22.08

Test for Heterogeneity:
Q(df = 2) = 44.1585, p-val < .0001

Model Results:

estimate      se     zval    pval    ci.lb   ci.ub
 -0.0598  0.5266  -0.1136  0.9095  -1.0920  0.9723


---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Figure 17: Mortality Odds Ratio for Centenarians in Developed Countries.

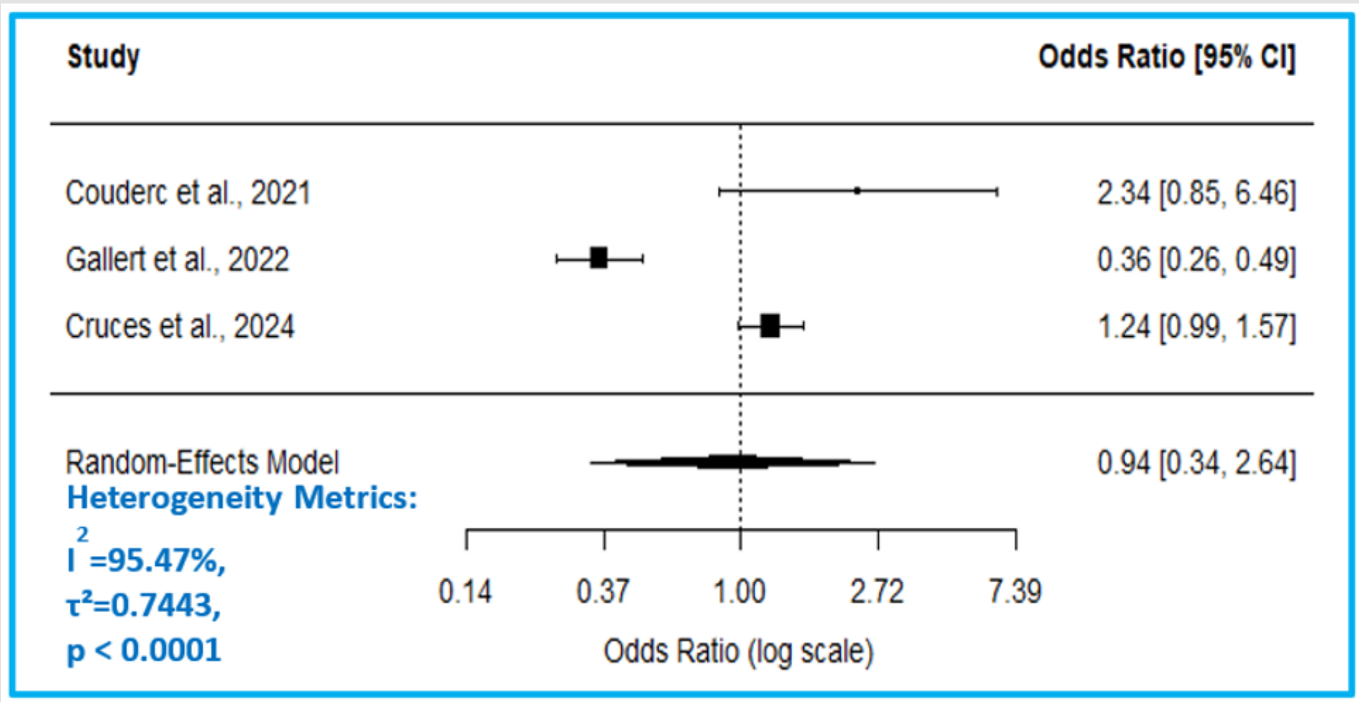

Figure 18: Mortality Odds Ratio Forest Plot for Centenarians in Developed Countries.

```
Random-Effects Model (k = 3; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.0010 (SE = 0.0017)
tau (square root of estimated tau^2 value):      0.0315
I^2 (total heterogeneity / total variability):   70.71%
H^2 (total variability / sampling variability):  3.41

Test for Heterogeneity:
Q(df = 2) = 6.8292, p-val = 0.0329

Model Results:

estimate      se    zval    pval    ci.lb   ci.ub
  0.0157  0.0236  0.6653  0.5059  -0.0306  0.0620

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Figure 19: Mortality Risk Difference for Centenarians in Developed Countries.

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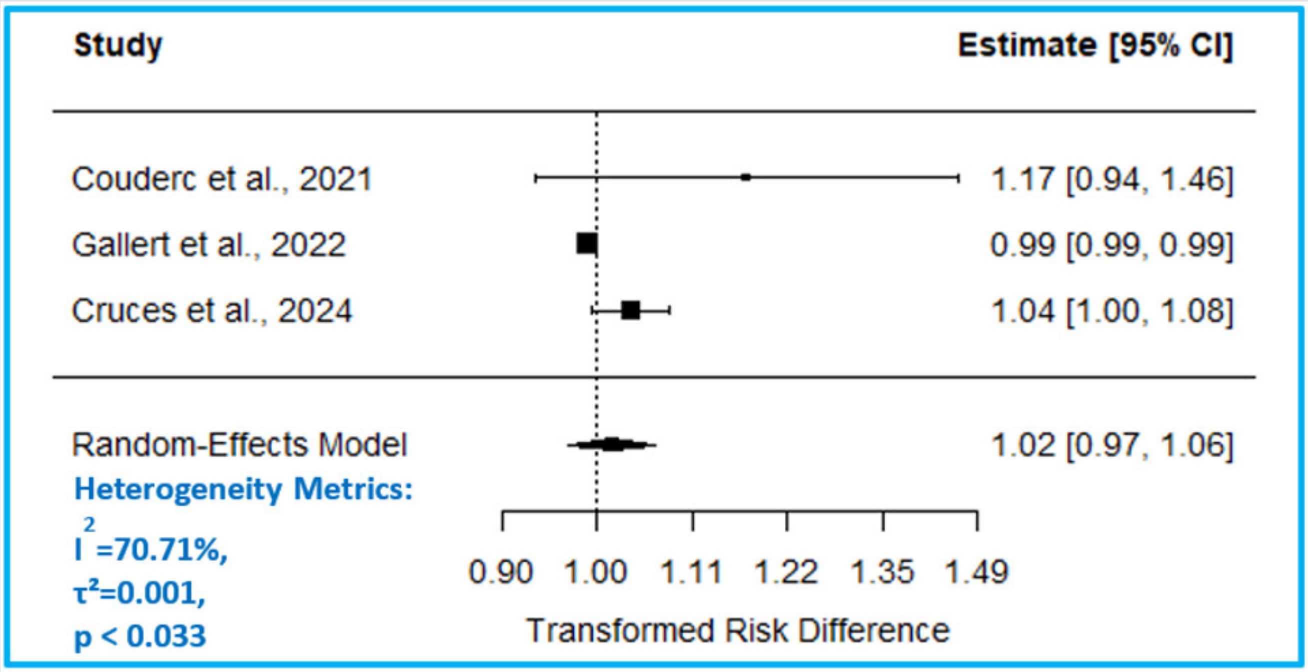

Figure 20: Mortality Risk Difference Forest Plot for Centenarians in Developed Countries.

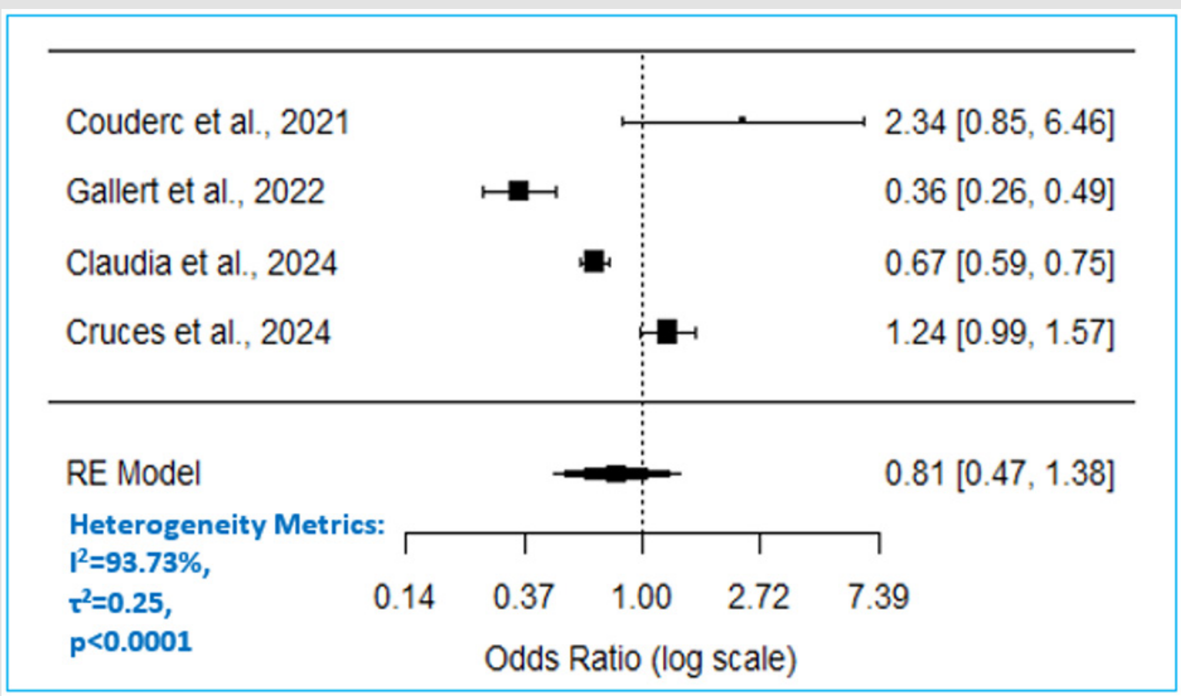

Figure 21: Forest Plot Depicting Pooled OR of COVID-19 Mortality.

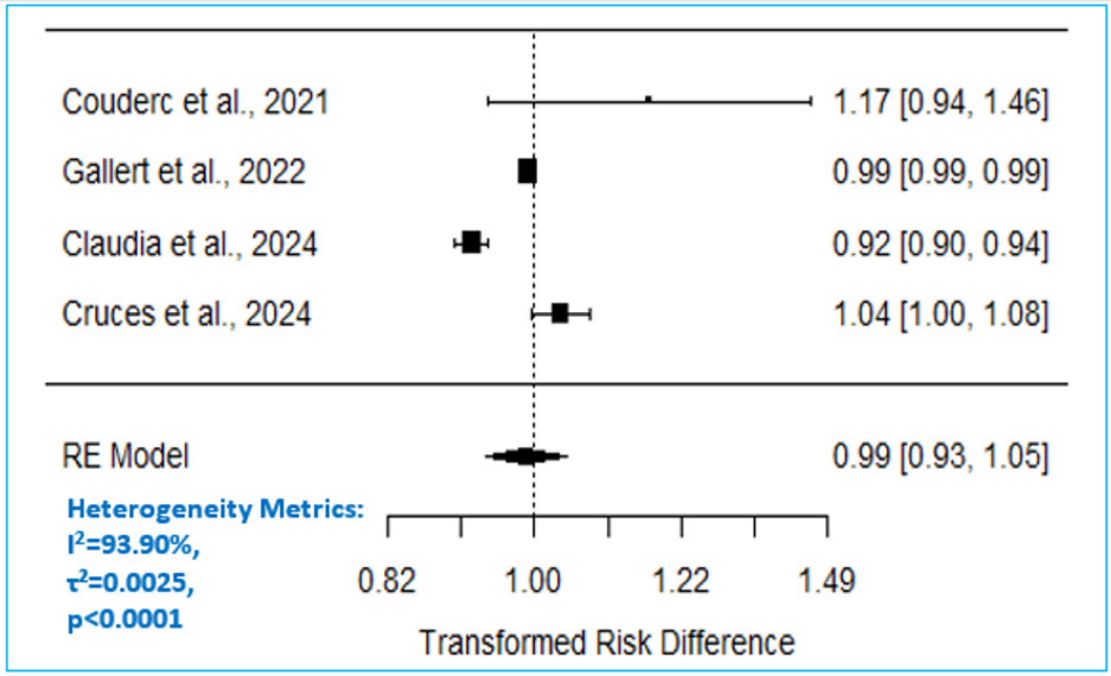

Figure 22: Forest Plot Depicting Risk Difference of COVID-19 Mortality.

Quality Assessment

The quality of studies was assessed using the Joanna Briggs Institute Critical Appraisal Checklist [13] for case-control, and cohort studies. Quality assessment of the studies included is accessible through Supplementary Material. All studies showed good quality.

Conclusion

We evaluated the proportion of mortality in centenarians diagnosed with COVID-19 during the pandemic. Based on the results, mortality rate within the centenarian subgroup is significant (0.24 CI 0.01-0.62), but among all participants, centenarians and non-centenarians, is insignificant (OR 0.81 CI (0.47-1.38), RD 0.99 CI (0.93-1.05)). A significantly higher mortality rate in centenarians following diagnosis with COVID-19 could likely be due to their age-related vulnerability, immunosenescence, or comorbidities. Couderc, et al. [26], found that centenarians with COVID-19 had a significantly higher mortality rate than non-centenarians (50% vs 21.3%, respectively), but a lower hospitalization rate, with most patients receiving supportive care in their nursing home. In the same study, centenarians also showed less symptoms, including asthenia, lower frequency fever and cough, but a higher frequency of geriatric syndromes such as delirium and falls. Also, 25% of centenarians experienced a worsening of pre-existing depression during their illness. Gellert, et al. [27], found that centenarians had lower rates of COVID-19-relevant hospital admissions compared to younger cohorts of oldest-old residents. However, COVID-19 hospital mortality was higher in female centenarians. Notably, none of the supercentenarians (≥110 years) had a recorded hospital admission for COVID-19.

The study also indicated an elevated risk of mortality for nonagenarians (those aged 90-99) and centenarians (100+) compared to octogenarians (80-89), and for men in general. The authors suggested that lower admission rates in centenarians might reflect different treatment priorities or more stringent infection prevention measures. Birchenall-Jiménez, et al. [28] found that 65.47% of the affected centenarians were female, and the overall mortality rate was 37.1%, with a significantly higher rate in males (45.24%) compared to females (32.83%). Kaplan-Meier survival analysis showed greater survival in females. The average time from symptom onset to recovery was 26.56 days, while to mortality was 14.33 days. The study also revealed that centenarians were concentrated in municipalities and emphasized the increased mortality among male centenarians and the need for extended follow-up due to prolonged recovery times. Cruces, et al. [29], found that centenarians had a higher proportion of COVID-19 cases compared to non-centenarians, however, centenarians appeared to exhibit extended survival after infection, with survival curves resembling those of 50-year-olds more than older age groups. No gender differences in survival were observed among centenarians, vaccination was found to have a strong protective effect and notably, infected centenarians were not prescribed more respiratory drugs (unlike non-centenarians).

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In the same study, centenarians showed reduced use of clinical resources, with fewer hospitalizations and emergency department visits, and no recorded ICU visits. The authors concluded that Basque centenarians showed more resistance to COVID-19 with better survival and less healthcare utilization.

Limitations

Couderc, et al. [26], The study had a limited number of centenarians (n=12), The small number of patients limited the ability to draw conclusions about the relationship between hospitalization rate and mortality rate and did not allow multivariable analysis to highlight factors influencing deaths or hospitalizations in this population. The centenarians studied were all living in nursing homes and might be more frail than community-dwelling centenarians. Moreover, The biological data was collected retrospectively from medical files, and C-reactive protein levels were missing for 26.2% of the residents, which could affect the conclusiveness of findings related to inflammation markers, overall recovery or mortality rates. Also, due to the small sample of centenarians and the lack of power of comparative analysis, few symptoms were significantly associated with age. Gellert, et al. [27]: Although the study analyzed a large number of centenarians, mortality rates may still lack statistical power for detecting smaller effects. The study notes that the vastly lower COVID-19-related hospital admission rates in centenarians could be due to the fact that they were treated differently, with a priority for ambulant treatment or more rigorous infection prevention measures, rather than inherent resilience. This suggests a limitation in directly interpreting lower admission rates as solely indicative of better resistance. Birchenall-Jiménez, et al. [28]: The absence of information on clinical comorbidities limits the ability to fully adjust for factors that might influence COVID-19-associated mortality.

The retrospective design (as in the abovementioned two studies) introduces potential biases related to the quality and accuracy of recorded data, as well as reliance on secondary records, which may affect the completeness and accuracy of the information, results and conclusions. Different categorization of municipalities and regions based on respective legislation, economic and geographical criteria may introduce variability that affects the interpretation of results at the regional level. The study notes that the age of centenarians did not appear to be a determining factor in survival but acknowledges that additional studies with larger samples are needed to confirm this finding. The study highlights the variability in the symptom-to-recovery window, suggesting the need for close monitoring, but this variability itself could be seen as a limitation in predicting individual outcomes. The study acknowledges that while the ethnic affiliation was predominantly mestizo and white, aligning with existing evidence of the Colombian population, this might limit the generalizability of findings to other ethnic groups. Cruces, et al. [29], The study notes that the findings regarding the response of centenarians to COVID-19 remain controversial in the broader literature, suggesting that the specific context of the Basque Country and the study's methodology might contribute to the observed results and could be a limitation in generalizing to all centenarian populations.

The study highlights that centenarians have a "younger" profile than the oldest non-centenarians, implying that comparisons between these groups might be influenced by these pre-existing differences beyond just age. In summary, common limitations across these studies include the retrospective nature of data collection, small sample sizes (especially in the Couderc et al. study), potential biases in data accuracy and completeness, and challenges in generalizing findings due to specific populations and geographical contexts. The lack of detailed information on comorbidities in some studies and the potential influence of different treatment approaches further contribute to the limitations in fully understanding the impact of COVID-19 on centenarians. Confounding factors like vaccination status, COVID-19 variants/waves, and treatment measures were not highlighted nor standardized in the studies, hence several inconsistencies may arise. Further research could group patients accordingly for better representation and accountability of results. Centenarians are a rare population, small sample size provide less precise estimates, more studies are needed in this demographic to better represent their health status and needs.

Recommendations

Future studies should aim for larger sample sizes to enable more robust statistical analyses, including multivariable analysis to identify specific factors influencing outcomes like mortality and hospitalization. Expanding studies beyond single-center designs to multi-center and potentially international collaborations could facilitate the inclusion of a more diverse range of centenarians, including those in different geographical locations and living situations (nursing homes vs. community-dwelling). As noted by Couderc, et al. [26], their small sample size limited their analysis. Future research could benefit from prospective and longitudinal study designs. This would allow for the standardized collection of detailed clinical, biological, and treatment data in real-time, reducing the potential for recall bias and missing information, such as detailed comorbidity data which was a limitation in the Birchenall-Jiménez, et al. [28] study. Future studies could delve deeper into differences within the centenarian population, such as comparing the experiences of those aged 100-105 with supercentenarians (≥110 years), as the Gellert, et al. [18], study hinted at potential differences, with no hospital admissions recorded for supercentenarians in their sample. Further investigation into gender-specific responses, as suggested by the differing mortality rates in male and female centenarians in the Colombian study and the higher hospital mortality in female centenarians in the German study, is also warranted.

Understanding the long-term effects of COVID-19 on centenarians is crucial. Future studies should include longitudinal follow-up

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to assess recovery trajectories, the persistence of symptoms, and the development of any long-term sequelae in this population. The Birchenall-Jiménez, et al. [28] study highlighted the prolonged recovery time, emphasizing the need for extended follow-up. As mentioned by Couderc, et al. [26], future research should explore the clinical and genetic specificities of centenarians in the context of COVID-19. This could involve investigating potential mechanisms of resilience observed in some centenarian populations, such as those in the Basque Country who showed extended survival, and the role of the immune system and inflammaging. Given the lower hospitalization rates observed in some studies and the preference for home hospitalization noted by Couderc, et al. [17], future research should evaluate the effectiveness of different treatment and care strategies specifically tailored for centenarians, considering the potential for different responses compared to younger older adults. Finally, to facilitate comparisons across different studies and enable better meta-analyses, future research would benefit from the standardization of data collection methods and definitions for symptoms, comorbidities, treatments, and outcomes. By addressing these areas, future studies can build upon the foundational knowledge provided by the current research to offer a more nuanced and comprehensive understanding of the impact of COVID-19 on centenarians, ultimately informing better prevention and management strategies for this unique and increasingly significant demographic group.

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Authors' contributions

Conceptualization: SI, WAEK-M, OMA, SC

Data curation: SI, WAEK-M, OMA

Formal analysis: SI, SC

Data investigation: SI, WAEK-M, OMA

Methodology: SI, WAEK-M, OMA, SC

Supervision: WAEK-M, SC

Writing – original draft: SI.

Writing – review & editing: SI, WAEK-M, OMA, SC

Conflict of Interests

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting the findings of this study are available as supplementary material file.

Institutional Review Board Statement. Not applicable.

Ethical Considerations

Ethical approval is not required for this protocol as it is a systematic review that includes secondary data from published studies. In this study, participants are not actively recruited, and data are not collected directly from them. The findings of the systematic review and meta-analysis will be disseminated through peer-reviewed publications.

Trial Registration

PROSPERO CRD645150; https://www.crd.york.ac.uk/PROSPERO/view/CRD42025645150

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