

Molo, Fabio; Pawel, Samuel; Fraga González, Gorka

**Working Paper**

## A Robustness Reproduction of "A Systematic Review and Meta-Analysis of 90 Cohort Studies of Social Isolation, Loneliness and Mortality"

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OCTOBER 2024

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# A robustness reproduction of “A systematic review and meta-analysis of 90 cohort studies of social isolation, loneliness and mortality” \*

Fabio Molo, Samuel Pawel, Gorka Fraga González

March 25, 2024

## Abstract

In a systematic review and meta-analysis, Wang et al. (2023) estimate the association of social isolation or loneliness with mortality outcomes. In their preferred analytical specification, the authors find an increased risk of mortality from all causes for both exposures: a pooled effect size for social isolation of 1.32; 95% confidence interval 1.26 to 1.39;  $P < 0.001$ ; a pooled effect size for loneliness of 1.14; 95% CI, 1.08 to 1.20;  $P < 0.001$ . We computationally reproduce these results by extracting data from the article PDF and re-implementing the original analysis, and we compare the extracted data with data that we later received from the authors. Second, we assess the robustness of the main results against plausible alternative analytic choices in three areas: estimation of the random effects models, heterogeneity, and adjustment for publication bias. We find that the main claims of the original authors are robust, although the majority of methods to adjust for publication bias suggest somewhat smaller effects than the original estimates.

**KEYWORDS:** meta-analysis, computational reproducibility, robustness reproduction

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The authors made the following contributions: FM: Conceptualization, Project administration, Supervision, Formal Analysis, Software, Investigation, writing – original draft; Writing – review & editing; SP: Conceptualization, Methodology, Formal Analysis, Software, Investigation, Writing – review & editing; GFG: Validation, Writing – review & editing

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We thank Abel Brodeur from the Institute for Replication for support and advice throughout the project.

Computer code to reproduce our analyses is available at <https://gitlab.uzh.ch/crsuzh/nhb-replication>.

## 1 Introduction

Wang et al. (2023) conducted a systematic review and meta-analysis of the associations between social isolation (SI) or loneliness with the risk of mortality outcomes in adults. In the present report, prepared as part of a collaboration between the Institute for Replication (Brodeur et al. 2024) and *Nature Human Behaviour* (Nature Human Behaviour 2024), we assess the computational reproducibility and the robustness of the main claim of the original paper (from the abstract):

*“[...] in the general population, both social isolation and loneliness were significantly associated with an increased risk of all-cause mortality (pooled effect size for social isolation, 1.32; 95% confidence interval (CI), 1.26 to 1.39;  $P < 0.001$ ; pooled effect size for loneliness, 1.14; 95% CI, 1.08 to 1.20;  $P < 0.001$ ).”*

We first investigate whether we can computationally reproduce the main claim (Section 2). Since we at first were unable to obtain either the raw data or the analysis code from the original authors, we semi-automatically extract the data from the article PDF and re-implement the described procedures using the statistical software R (R Core Team 2024, v. 4.4) instead of the Stata 14.2 software used in the original study.<sup>1</sup> The data extracted in this way is identical to the data we later received from the original authors.

In Section 3, we then analyze the main claim’s robustness to the following plausible alternative analytic choices: (1) using restricted maximum likelihood (REML) instead of the DerSimonian and Laird method to estimate the heterogeneity variance, (2) varying the original threshold of estimated heterogeneity (the  $I^2$  statistic) that determines whether a fixed effect or a random effects model is used, and (3) adjusting for publication bias with alternative methods to the original’s trim-and-fill analysis.

All our steps were pre-specified and registered at the Institute for Replication in a protocol available along with the analytic code and a containerized reproducible environment at our public repository at <https://gitlab.uzh.ch/crsuzh/nhb-replication>.

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<sup>1</sup>This type of analysis is sometimes referred to as a test of “recreate reproducibility” (Dreber and Johannesson 2024) rather than of computational reproducibility, which would require access to original code and data.

## 2 Computational Reproducibility

The original data is declared to be “*available from the corresponding author upon request*” (Wang et al. 2023, p.1315) (cf. the journal’s [guidelines](#)). For ca. two months, following attempts by the Institute for Replication as well as the Nature Human Behaviour editor, we obtained no code and no raw data. Therefore, we semi-automatically extracted the analysis data from Figure 2 in the original article using the R package `tabulapdf` (Sepulveda 2024).

We then re-implemented the original meta-analysis using the R package `metafor` (Viechtbauer 2010, v. 4.6-0). We did this within a containerized reproducible environment based on the Rocker project (Boettiger and Eddelbuettel 2017) across two different operating systems (Ubuntu Linux 22.04 and Windows 11).

Upon completion of this computational reproduction we received the original data from the authors. The obtained data is identical to the data extracted from the PDF up to rounding of effect sizes on the second decimal place. It additionally contains information necessary for the various subgroup and sensitivity analyses in the original paper. Since the original authors do not publicly share their data we base the remainder of our report on the data that was extracted from the PDF.

In this way, we were able to recreate the main claim, i.e., the reported pooled effect estimates (risk or hazard ratios), 95% confidence intervals, and  $p$ -values for all-cause mortality, which are 1.32; 95% CI from 1.26 to 1.39;  $p < 0.0001$  for social isolation and 1.14; 95% CI from 1.08 to 1.20;  $p < 0.0001$  for loneliness. Figure 1 in Section 5 reproduces Figure 2 in Wang et al. (2023), i.e., the forest plots of the individual study estimates along with the pooled estimates.

Table 1 in Section 6 summarizes the computational reproducibility of the materials provided by the original authors. The data obtained from the authors of the meta-analysis consists in effect estimates and confidence intervals of each underlying individual study (in part pooled or unpooled based on demographic characteristics of the study populations) for the different outcomes on a common scale, as well as information about the adjustment variables used in each individual study.

### 3 Robustness Reproduction

Next we assess how robust the two pooled effect estimates and 95% confidence intervals (CIs) are to plausible alternative analytic decisions than those of the original authors. As we specified in our protocol prior to our replication, we consider an effect estimate and CI to be *qualitatively different* from the original analysis if the CI does include an effect size of 1 (i.e., “no increase in risk”) or if the effect goes in the opposite direction, and *quantitatively different* from the original analysis if the original CI and the CI based on the new analysis do not overlap.

We consider plausible alternative analytic choices in three areas: estimation of the random effects models, heterogeneity, and adjustment for publication bias. Figure 2 in Section 5 and Table 2 in Section 6 summarize the resulting pooled effect size estimates.

#### 3.1 Estimation method

To estimate the total pooled effect, the original authors used a two step procedure: 1) They determined presence of heterogeneity with Cochran’s  $Q$  test at significance level 0.1 and quantified it with the  $I^2$  statistic. 2) An  $I^2 < 50\%$  was interpreted as “low heterogeneity” and in this case the authors used a fixed-effect model, while  $I^2 \geq 50\%$  was interpreted as “high heterogeneity” and in this case they used a random effects model with estimation method “DerSimonian and Laird” (Wang et al. 2023, p. 1314, Statistical methods). We repeat the two step procedure but use restricted maximum likelihood (REML) instead of DerSimonian and Laird estimation of the heterogeneity variance, because REML is at least a plausible alternative estimation method due to its statistical properties (Veroniki et al. 2015, Langan et al. 2018).

The resulting pooled effect estimates, CIs, and  $p$ -values for all-cause mortality are 1.34; 95% CI from 1.27 to 1.42;  $p < 0.0001$  for social isolation and 1.14; 95% CI from 1.09 to 1.19;  $p < 0.0001$  for loneliness. We therefore find the reported pooled effect estimates to be both qualitatively and quantitatively robust to the choice of REML instead of DerSimonian and Laird estimation.

### 3.2 Varying the threshold for heterogeneity

With respect to heterogeneity as estimated by  $I^2$ , the original analysis used a threshold of  $c = 50\% = 0.5$  in their two step procedure as described in the previous section. we repeat the two step procedure for different thresholds  $c = 0.1, 0.2, \dots, 0.8, 0.9$ . For each  $c$ , we compute the pooled effect estimate and CI to see how robust the result is to the choice of  $c$ . To estimate  $I^2$  we use the same estimation method as in the original analysis (DerSimonian and Laird).

The original estimates are robust across different thresholds up to  $c = 0.8$  for isolation, above which the estimate is 1.24; 95% CI from 1.22 to 1.26;  $p < 0.0001$ , and up to and including  $c = 0.9$  for loneliness, for which the estimate remains at 1.14; 95% CI from 1.08 to 1.20;  $p < 0.0001$ . In our judgment, such a threshold would no longer be a plausible analytic choice. We therefore conclude that the original results are robust regarding the heterogeneity threshold.

The results also remain robust against not applying a threshold at all. Using a test for heterogeneity to choose between a random effects and a fixed effect model and interpreting the  $I^2$  statistic as an absolute measure of heterogeneity, are known as problematic in the literature (Borenstein et al. 2017, 2019). Instead, the recommendation is to base the model choice on substantive knowledge about the studies, and to only use a fixed-effect model if all studies in the analysis are essentially replications of each other. To us, this does not seem obvious for the studies from Wang et al. (2023) as the studies were conducted in different countries, populations, time periods, and their effect estimates were adjusted for different confounders. We therefore consider a random effects model, estimated with REML, regardless of whether the  $Q$  test and  $I^2$  approach indicates heterogeneity, to be a plausible analytic choice. Because  $I^2$  was above the original threshold of  $c = 0.5$  both for isolation and for loneliness, this approach results in the same robust estimates from Section 3.1.

### 3.3 Adjustment for publication bias

The original authors assessed publication bias using Egger's and Begg's tests (Wang et al. 2023, p. 1315, Statistical methods), concluding presence of publication bias when the corresponding  $p$ -values are both below 0.05. In this case, they report



results adjusted for publication bias using the “trim-and-fill” method from [Duval and Tweedie \(2000\)](#).

We first computationally reproduce the original authors’ tests for publication bias ([Wang et al. 2023](#), p. 1308). For Egger’s test (assuming the original authors use the “classical” version from [Egger et al. \(1997\)](#)) we reproduce the original  $p$ -values for social isolation ( $p = 0.006$ ) and for loneliness ( $p = 0.46$ ). For Begg’s test we reproduce the original  $p$ -values (to close approximation) of  $p = 0.018$  and  $p = 0.023$ , respectively. We also reproduce the original estimates for the trim-and-fill analysis (1.23; 95% CI from 1.17 to 1.29;  $p < 0.0001$ ), which the original authors only conducted for social isolation and reported in Supplementary Table 11.

There are various alternative methods to adjust for publication bias and a common recommendation is to use a triangulation approach: apply different methods and see whether they lead to similar results ([Vevea et al. 2019](#)). Additionally to the trim-and-fill analysis, we therefore compute effect estimates and CIs based on three different adjustment methods as robustness checks (summarized in Figure 2). We do this both for social isolation and loneliness, given that the results from the original Egger’s and Begg’s tests make it at least plausible that there is some publication bias for both these exposures.

The first method is a form of linear regression adjustment based on the classical version of Egger’s test, and corresponds to the “Precision-Effect-Test” (PET) described in [Stanley and Doucouliagos \(2014\)](#). We obtain an adjusted effect estimate of 1.18; 95% CI from 1.13 to 1.24;  $p = 0.006$  for social isolation. This estimate points in the same direction as the original estimate, but it is lower and its CI does not overlap with the original estimate’s. For the loneliness exposure, the PET adjusted estimate is 1.09; 95% CI from 1.02 to 1.17;  $p = 0.46$ , which is also lower than the original, but with overlapping CI.

Next we use the [Henmi and Copas \(2010\)](#) method to obtain effect estimates adjusted for publication bias.<sup>2</sup> The resulting estimates are 1.24; 95% CI from 1.13 to 1.36 for social isolation and 1.11; 95% CI from 1.00 to 1.24 for loneliness. For both exposures, these estimates are lower than the original estimates but their CIs overlap with the original CIs.

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<sup>2</sup>The Henmi method simultaneously uses an alternative estimation method to DerSimonian and Laird discussed in Section 3.1 and thus provides an additional robustness check.

Finally we adjust for publication bias using a selection model, which models the publication of a study (or more precisely, the mechanism of a study being selected for publication) as a function of its  $p$ -value. Based on the method described by [Hedges \(1992\)](#) and others we model the selection mechanism with a step function, and we choose steps at 0.05 and 1 for two-sided  $p$ -values. This assumes that the likelihood of publication of a study may be different if the two-sided  $p$ -value is below 0.05 than if it is above this common “significance” threshold; that the likelihood is constant within these two intervals; and that this is the case both if a study estimates a positive effect or a negative effect of the exposure on all-cause mortality. The resulting estimate for social isolation is 1.29; 95% CI from 1.20 to 1.38;  $p < 0.0001$  – again lower than the original but with overlapping CI. For loneliness, the estimate based on the selection model is 1.17; 95% CI from 1.10 to 1.25;  $p < 0.0001$ , which is higher than the original, but also with overlapping CI.

To summarize, all adjustments for publication bias, with the sole exception of the selection model adjustment for the loneliness exposure, result in lower point estimates for the pooled effects of social isolation or loneliness than the original estimates. For social isolation, all CIs do not include 1 (which would be interpreted as “no increased risk”), and the PET method is the only one whose CI does not overlap with the original CI. For loneliness, the Henmi Copas CI is the only one that (marginally) includes 1, and all CIs overlap with the original CIs. By combining these results we conclude that the original results are qualitatively and quantitatively robust to different adjustment methods, even though these methods suggest a somewhat lower effect than the original.

## 4 Conclusion

Taken together, our robustness reproduction of Wang et al. (2023) shows that its main claims can be computationally reproduced by extracting the data from the article PDF and re-implementing the described procedures in R, as well by doing the same using data later obtained from the original authors. Further, it shows that these claims are qualitatively and quantitatively robust against plausible alternative choices regarding estimation of the random effects models and study heterogeneity. The claims are also robust against different methods of adjusting for publication bias, though a majority of these methods suggest the effects may be somewhat smaller than estimated in the original article. The analytic code and a reproducible environment for our analyses is available at <https://gitlab.uzh.ch/crsuzh/nhb-replication>.

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## 5 Figures

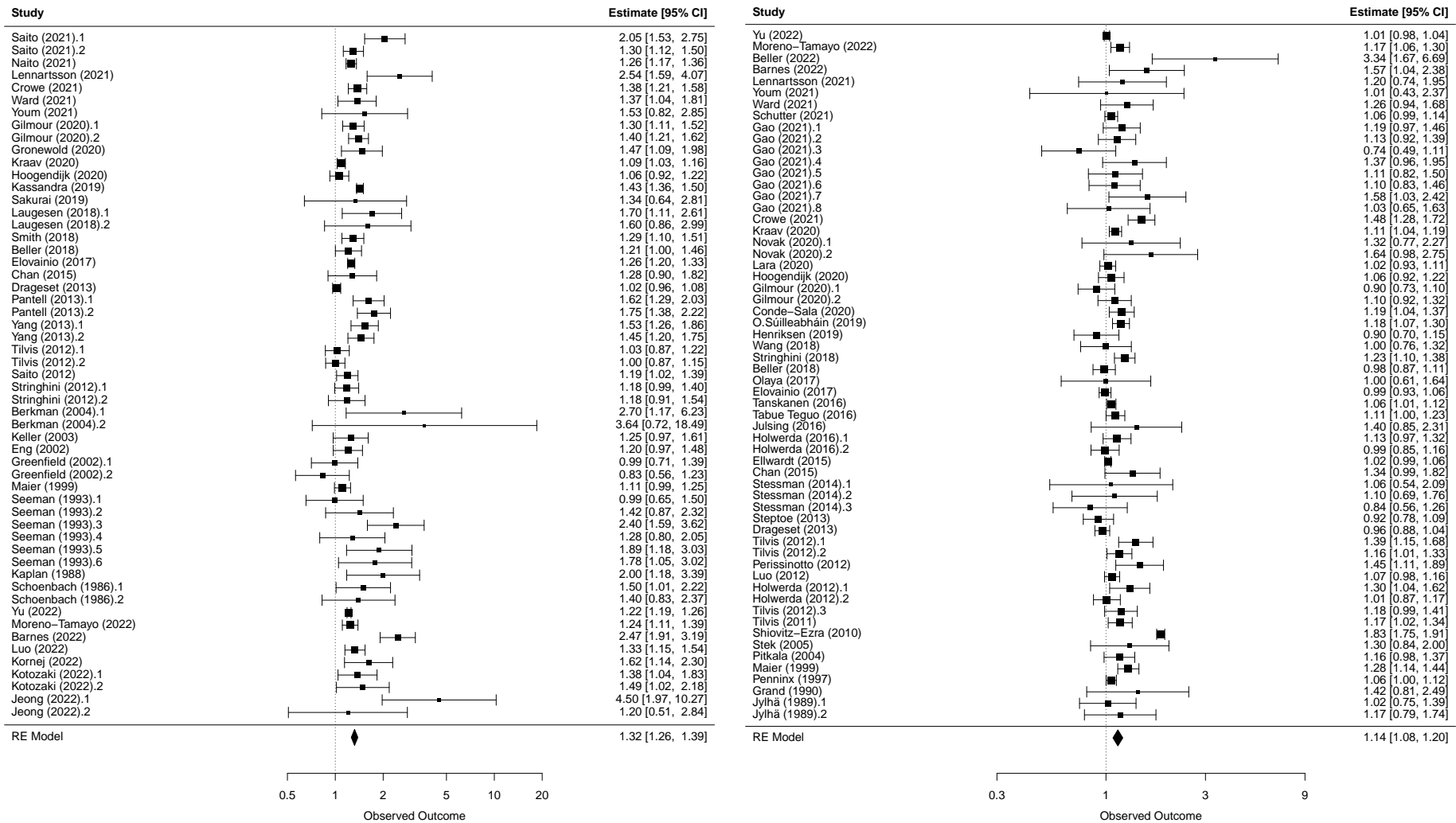


Figure 1: Computational reproduction of Figure 2 in Wang et al. (2023). The left-hand side reports the association of social isolation and risk of all-cause mortality, the right-hand side the association of loneliness and risk of all-cause mortality.

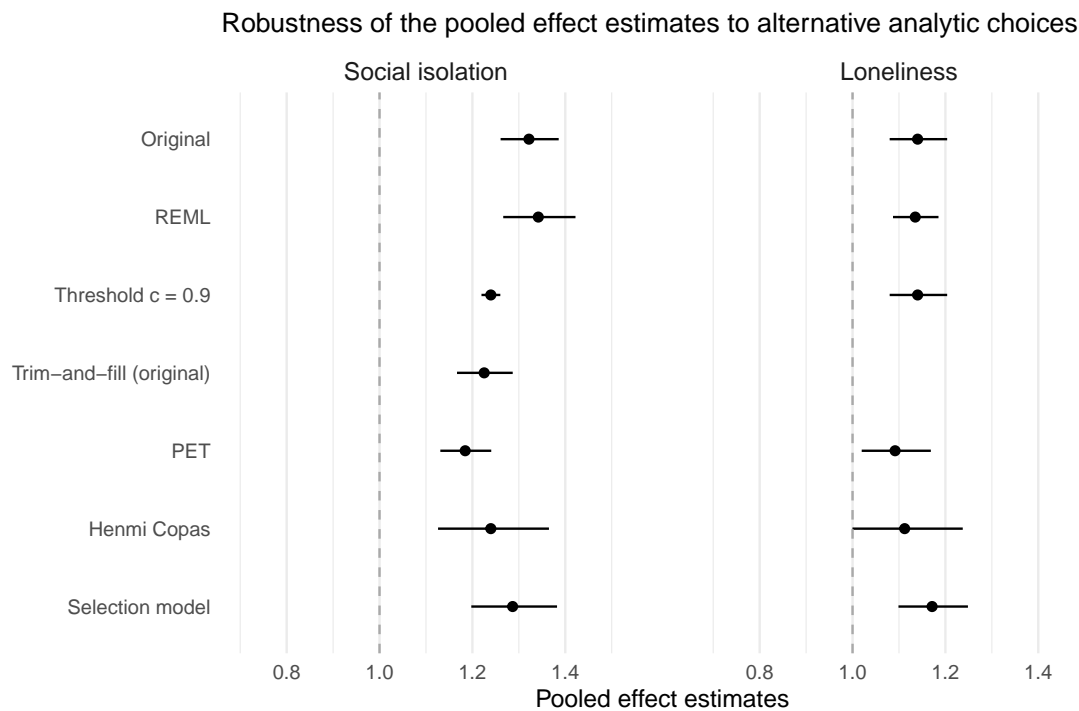


Figure 2: Summary of all robustness checks. The original effects are robust to different random effects model estimation (REML) and different heterogeneity thresholds. Alternative methods to adjust for publication bias (PET, Henmi Copas, Selection model) suggest slightly lower effects, but point in the same direction and the 95% confidence intervals overlap with those from the original.



## 6 Tables

Table 1: Replication Package Contents and Reproducibility

Replication Package Item	Fully	Partial	No
Raw data provided	✓		
Analysis data provided	✓		
Cleaning code provided			✓
Analysis code provided			✓
Reproducible from raw data	✓		
Reproducible from analysis data	✓		

*Notes:* This table summarizes the replication package contents contained in [Wang et al. \(2023\)](#). We consider the original results to be fully computationally reproducible from data even though at first (for ca. two months) no data was shared. In a meta-analysis the distinction between “raw data” and “analysis data” is not clear. We consider the obtained data (both from the article PDF and, later, from the original authors) to represent both.

Table 2: Summary of all robustness checks

Exposure	Method	Estimate	CI lower	CI upper	p-value
Social isolation	Original	1.32	1.26	1.39	< 0.0001
Social isolation	REML	1.34	1.27	1.42	< 0.0001
Social isolation	Threshold $c = 0.9$	1.24	1.22	1.26	< 0.0001
Social isolation	Trim-and-fill (original)	1.23	1.17	1.29	< 0.0001
Social isolation	PET	1.18	1.13	1.24	0.006
Social isolation	Henmi Copas	1.24	1.13	1.36	NA
Social isolation	Selection model	1.29	1.20	1.38	< 0.0001
Loneliness	Original	1.14	1.08	1.20	< 0.0001
Loneliness	REML	1.14	1.09	1.19	< 0.0001
Loneliness	Threshold $c = 0.9$	1.14	1.08	1.20	< 0.0001
Loneliness	Trim-and-fill	1.23	1.17	1.29	< 0.0001
Loneliness	PET	1.09	1.02	1.17	0.46
Loneliness	Henmi Copas	1.11	1.00	1.24	NA
Loneliness	Selection model	1.17	1.10	1.25	< 0.0001

Summary of all robustness checks, as displayed in [Figure 2](#).

## Computational environment

The following R environment was used to produce the results in this report.

```
sessionInfo()

## R version 4.4.1 (2024-06-14)
## Platform: x86_64-pc-linux-gnu
## Running under: Ubuntu 22.04.4 LTS
##
## Matrix products: default
## BLAS:   /usr/lib/x86_64-linux-gnu/blas/libblas.so.3.10.0
## LAPACK: /usr/lib/x86_64-linux-gnu/lapack/liblapack.so.3.10.0
##
## locale:
##  [1] LC_CTYPE=en_US.UTF-8      LC_NUMERIC=C
##  [3] LC_TIME=de_CH.UTF-8      LC_COLLATE=en_US.UTF-8
##  [5] LC_MONETARY=de_CH.UTF-8  LC_MESSAGES=en_US.UTF-8
##  [7] LC_PAPER=de_CH.UTF-8     LC_NAME=de_CH.UTF-8
##  [9] LC_ADDRESS=de_CH.UTF-8   LC_TELEPHONE=de_CH.UTF-8
## [11] LC_MEASUREMENT=de_CH.UTF-8 LC_IDENTIFICATION=de_CH.UTF-8
##
## time zone: Europe/Zurich
## tzcode source: system (glibc)
##
## attached base packages:
## [1] stats      graphics  grDevices  utils      datasets  methods   base
##
## other attached packages:
## [1] ggplot2_3.5.1      metafor_4.6-0      numDeriv_2016.8-1.1
## [4] metadat_1.3-0      Matrix_1.6-5       dplyr_1.1.4
## [7] tabulapdf_1.0.5-3  knitr_1.48
##
## loaded via a namespace (and not attached):
##  [1] bit_4.0.5          gtable_0.3.5       crayon_1.5.3       highr_0.11
##  [5] compiler_4.4.1     tidyselect_1.2.1   parallel_4.4.1     scales_1.3.0
##  [9] png_0.1-8          lattice_0.22-5     readr_2.1.5        R6_2.5.1
## [13] labeling_0.4.3     generics_0.1.3     tibble_3.2.1       munsell_0.5.1
## [17] pillar_1.9.0       tzdb_0.4.0         rlang_1.1.4        utf8_1.2.4
## [21] mathjaxr_1.6-0     xfun_0.46.8        bit64_4.0.5        cli_3.6.3
## [25] withr_3.0.1        magrittr_2.0.3     grid_4.4.1         vroom_1.6.5
## [29] rJava_1.0-6        hms_1.1.3          lifecycle_1.0.4    nlme_3.1-165
## [33] vctrs_0.6.5        evaluate_0.24.0    glue_1.7.0         farver_2.1.2
## [37] fansi_1.0.6        colorspace_2.1-1   tools_4.4.1        pkgconfig_2.0.3

cat(paste(Sys.time(), Sys.timezone(), "\n"))

## 2024-09-11 14:40:16.06055 Europe/Zurich
```