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Review article

The midlife health penalty: A systematic review and meta-analysis of loneliness and health-related quality of life in adults aged 40–65

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ABSTRACT

Loneliness is a recognised determinant of morbidity and mortality in older populations, but its association with health-related quality of life during middle adulthood remains less clearly defined. This systematic review and meta-analysis quantified the association between loneliness and mental and physical health-related quality of life among community-dwelling adults aged 40–65 years and examined whether associations varied by study design and demographic characteristics. Observational cross-sectional and longitudinal studies were identified through electronic searches of EBSCOhost, ScienceDirect, Scopus, and Web of Science, supplemented by citation chaining. Seventeen independent studies were included. Random-effects models showed that loneliness was associated with poorer mental health-related quality of life (pooled correlation 0.42; 95% confidence interval 0.35 to 0.49) and poorer physical health-related quality of life (pooled correlation 0.19; 95% confidence interval 0.12 to 0.26). Heterogeneity was substantial in both domains, indicating that pooled estimates should be interpreted as average associations across diverse populations, measures, and outcomes. Study design moderated mental health findings, with longitudinal studies showing stronger associations than cross-sectional studies. Gender composition and the prevalence of marriage or partnership also explained some of the between-study variation. Evidence for small-study effects was mixed. Findings suggest that loneliness in midlife is meaningfully associated with poorer mental and physical health-related quality of life, although stronger longitudinal and cross-cultural evidence is needed. Midlife loneliness assessment may be considered as part of a broader psychosocial risk evaluation.

1. Introduction

Loneliness has emerged as a pressing global public health concern, with mortality risks comparable to well-established clinical indicators [1]. Recent estimates suggest that loneliness contributes to approximately 871,000 deaths annually, highlighting a mortality burden that rivals smoking and obesity [2]. The impact of social disconnection on longevity is profound: social isolation and loneliness are associated with a 26% greater risk for all-cause mortality [3], a 30% increased likelihood of cardiovascular events [4,5], and a 50% higher risk of dementia [6]. Consequently, loneliness is no longer viewed merely as a distressed emotional state, but as a critical determinant of physical functioning and Health-Related Quality of Life (HRQoL) [7].

Despite this robust evidence base, the current literature is heavily skewed toward geriatric populations. While the "health penalty" of loneliness among older adults is well documented, the implications for middle-aged adults (ages 40–65) remain insufficiently understood. This represents a critical evidentiary gap. Middle adulthood is a distinct developmental period often characterised by peak social responsibility, the so-called "sandwich generation" managing careers, ageing parents, and dependent children. Loneliness during this life stage may be particularly toxic, serving as a period of "incubation" in which the physiological wear-and-tear of social disconnection begins to accumulate [8], eventually manifesting as overt chronic disease in later life. Understanding the association between loneliness and HRQoL in this demographic is therefore essential for early intervention and the preservation of healthy ageing trajectories.

It is necessary to distinguish between social isolation and loneliness. While often conflated, they represent distinct phenomena: social isolation is the objective state of having few social roles or interactions, whereas loneliness is the distress resulting from a discrepancy between what is desired and actual social connections [2]. Crucially, an individual can be objectively integrated into a social network yet experience profound subjective loneliness [9]. It is this subjective perception of

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disconnection that often drives a decline in quality of life.

HRQoL serves as a vital metric in this context, capturing an individual's perceived functioning across physical, psychological, and social domains [2]. Existing research suggests that loneliness corrodes these domains via multiple pathways, including increased perceived stress [10], immune dysfunction [11], and the exacerbation of depression and anxiety [12–14]. However, the magnitude of these associations, specifically within the midlife cohort, has not been systematically synthesised.

To address this gap, this study provides the first systematic review and meta-analysis specifically evaluating the association between loneliness and HRQoL among middle-aged adults. The primary objective is to quantify the strength of the relationship between loneliness and both mental and physical HRQoL domains in adults aged 40–65. Secondarily, we aim to identify key moderators (including gender, geographic region, and study design) that influence these associations, and to assess the methodological consistency of the existing evidence base. By shifting the focus upstream from the geriatric to the midlife population, this review aims to inform more timely public health interventions that can mitigate the long-term health burdens of loneliness.

2. Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was informed by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidance. The study protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD420251016561). The protocol prespecified the target population, primary outcomes, synthesis models, and moderator framework.

3. Search strategy and information sources

A comprehensive electronic search was conducted in EBSCOhost, ScienceDirect, Scopus, and Web of Science from database inception to June 2025. The search strategy was restricted to English-language publications and combined controlled vocabulary and free-text terms related to loneliness, social disconnection, middle adulthood, health-related quality of life, mental health, physical health, and biomarkers. To minimise publication bias and ensure comprehensive coverage, the electronic search was supplemented with backward and forward citation chaining of included articles and relevant reviews.

3.1. Eligibility criteria

Studies were selected based on the following inclusion criteria:

Studies were eligible if they included community-dwelling or general adult populations in middle adulthood (ages 40–65) and reported a quantitative measure of loneliness, such as the UCLA Loneliness Scale or a single-item loneliness measure. Loneliness was defined as the subjective distress arising from a perceived discrepancy between desired and actual social relationships. Studies measuring objective social isolation without a subjective loneliness component were excluded to maintain conceptual distinctness. Eligible studies also reported a measure of health-related quality of life in either the mental domain (e.g., depressive symptoms, life satisfaction, WHOQOL-mental) or the physical domain. The physical domain was operationalised broadly to include subjective measures (e.g., self-rated health, WHOQOL-physical, mobility/IADL) and objective physiological indicators (e.g., blood pressure and inflammatory markers such as IL-6 and CRP). Quantitative cross-sectional and longitudinal/cohort designs were included. Qualitative reports, reviews, and studies lacking extractable correlation data were excluded.

3.2. Study selection and data extraction

Records were imported into Covidence for duplicate removal, title and abstract screening, and full-text review. Three reviewers independently screened titles and abstracts against eligibility criteria, followed by full-text assessment. Disagreements were resolved through consensus.

Data extraction was performed independently by two reviewers using a piloted extraction form. The following variables were extracted: country/region, study design, sample size (N), gender composition (% female), marital/partnership prevalence (% married/partnered), loneliness measure, outcome measure, and effect-size information. Information on measurement instruments was codified by family (e.g., UCLA variants, single-item measures) for moderator analysis. To ensure independence of effects, when studies reported data from distinct waves or non-overlapping subsamples, these were treated as separate analytic entries; otherwise, the most fully adjusted correlation available was prioritised.

3.3. Effect size computation and synthesis

The primary effect size was Pearson's correlation coefficient (r). To stabilise variances for analysis, all correlations were converted to Fisher's z scale using the formula $z = 0.5 \times \ln((1 + r)/(1-r))$ with variance $V_z = 1/(n-3)$. Results were back-transformed to r for presentation. For outcome measures where higher scores indicated better health (e.g., Life Satisfaction), correlations were reverse-scored to ensure that positive effect sizes consistently reflected an association between higher loneliness and poorer health.

Separate random-effects meta-analyses were conducted for mental and physical health outcomes using inverse-variance weighting and Restricted Maximum Likelihood (REML) estimation. The random-effects model was selected a priori to account for anticipated between-study heterogeneity resulting from diverse populations and measurement tools. Because the number of physical health studies was limited, subjective physical health indicators and objective physiological indicators were pooled as a broad physical-health domain and interpreted cautiously as indicators of physical health burden rather than as interchangeable endpoints. Heterogeneity was assessed using Cochran's Q statistic, the I2 statistic (quantifying the proportion of total variance due to heterogeneity), the between-study variance ($\tau 2$), and 95% prediction intervals (PIs).

3.4. Moderator and sensitivity analyses

To investigate sources of heterogeneity, random-effects meta-regression models were fitted.

a. **Mental Health Models:** Moderators included study design (longitudinal vs. cross-sectional), gender composition, marital status prevalence, loneliness instrument family, and geographic region.
b. Physical Health Models: Moderators included study design, gender composition, and marital status prevalence. Geographic region, loneliness instrument type, and physical-outcome type were not modelled in the physical domain because the number of studies per subgroup was insufficient to produce stable estimates ($k < 10$).

For each model, the proportion of between-study variance explained (R^2 analogue) was reported alongside the omnibus test of moderators (Q_M).

3.5. Publication bias and small-study effects

Small-study effects were assessed via visual inspection of funnel plots and statistical tests, contingent on having adequate numbers of studies. For the mental health domain, Egger's regression test and the Duval and

Tweedie trim-and-fill procedure were applied. For the physical health domain, Egger's test, Begg's test, and Rosenthal's Classic Fail-Safe N were utilised. Because funnel plot asymmetry can arise from heterogeneity as well as publication bias, small-study diagnostics were interpreted alongside heterogeneity and sensitivity analyses.

3.6. Software

All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) software version 3.

4. Results

4.1. Study selection

The systematic search strategy across EBSCOhost, ScienceDirect, Scopus, and Web of Science yielded 458 records, supplemented by 10 records from citation chaining. After removing 149 duplicates in Covidence, 314 records were screened by title and abstract. Of these, 142 full-text articles were assessed for eligibility. A total of 125 studies were excluded at the full-text stage, primarily due to ineligible study designs ($n = 31$) or irrelevant outcomes ($n = 37$). Ultimately, 17 independent analytic entries met the inclusion criteria. The selection process is detailed in the PRISMA flow diagram.

4.2. Study characteristics

The included analytic entries (k = 17) represented diverse middle-aged populations from North America ($n = 7$), Europe ($n = 6$), and Asia ($n = 4$). No African study was identified among the included entries, highlighting an important geographic gap. The cumulative sample sizes were $N = 21{,}777$ for the mental health analysis and $N = 7292$ for the physical health analysis. Seven entries contributed data to both domains. The evidence base included cross-sectional (k = 8) and longitudinal/cohort (k = 9) entries. Loneliness was most frequently assessed using variants of the UCLA Loneliness Scale (n = 7), followed by single-item or author-derived measures. No included entry used the De Jong Gierveld Loneliness Scale as the primary measure of loneliness.

A random-effects meta-analysis of k = 14 studies examined the relationship between loneliness and mental health. The analysis revealed a significant, moderate-to-strong positive association between loneliness and poor mental health outcomes ($r = 0.42$; 95% CI: 0.35 to 0.49; $p < 0.001$).

Substantial heterogeneity was observed (Q = 111.41, $p < 0.001$; I2 = 88.33%). This indicates that the pooled estimate should be interpreted as an average association across diverse populations, measurement instruments, and mental health outcomes rather than as a uniform effect. Visual inspection of the funnel plot suggested asymmetry, and Egger's regression test was significant ($p = 0.001$). However, the Duval and Tweedie trim-and-fill analysis imputed zero missing studies. These findings were therefore interpreted as mixed evidence regarding small-study effects rather than definitive evidence of publication bias.

4.3. Meta-analysis of loneliness and physical health HRQoL

A random-effects meta-analysis of k = 10 studies assessed the association between loneliness and physical health. The analysis demonstrated a significant positive association between loneliness and physical health detriments ($r = 0.19$; 95% CI: 0.12 to 0.26; $p < 0.001$).

High heterogeneity was present (I2 = 84.88%), again indicating meaningful between-study variation in effect sizes. Publication bias diagnostics indicated no substantial small-study effect for the physical domain (Egger's $p = 0.40$), and the Classic Fail-Safe N indicated that 562 null studies would be required to overturn the finding. Leave-one-out sensitivity analyses indicated that no single study disproportionately influenced the pooled effect sizes for either mental or physical health; the summary effects remained statistically significant and within the 95% confidence intervals of the original models upon the exclusion of any individual study.

5. Moderator analyses

Random-effects meta-regressions were conducted to explore heterogeneity (Table 3). (See Figs. 1–5.) (See Tables 1 and 2.)

For mental health, study design was a significant moderator (QM = 32.85, $p < 0.001$), explaining 81% of the between-study variance (R2 = 0.81). Longitudinal studies showed stronger associations than cross-sectional designs. Gender composition significantly moderated both mental ($p = 0.004$) and physical health outcomes ($p = 0.040$), although the directions differed by domain and should be interpreted cautiously, as these are study-level meta-regression estimates. For physical health, marital or partnership prevalence was also a significant moderator ($p = 0.028$; R2 = 0.55), suggesting that relationship context may partly explain between-study variation in the loneliness-physical health association.

6. Discussion

This systematic review and meta-analysis synthesised quantitative evidence on the association between loneliness and health-related quality of life among middle-aged adults (ages 40–65). While the health risks of loneliness are well-documented in geriatric populations, our results indicate that midlife represents an important and under-examined window of vulnerability. Loneliness in midlife was associated with poorer mental health (r = 0.42) and, more modestly, with physical health detriments ($r = 0.19$). These findings suggest that the health burden of social disconnection is already detectable before old age.

The substantial heterogeneity observed in both domains has important implications for interpretation. The pooled estimates represent average associations across studies that differed in design, population characteristics, loneliness instruments, outcome measures, and follow-up periods. Therefore, the findings should not be interpreted as evidence of a single, uniform association between loneliness and health-related quality of life across all middle-aged adults. Rather, they indicate a consistent direction of association whose magnitude varies meaningfully across contexts.

A notable finding from our moderator analysis was that longitudinal studies yielded stronger effect sizes for mental health than cross-sectional designs. This pattern differs from the common expectation that cross-sectional correlations may be inflated by common method variance. In the context of loneliness, however, it may reflect a chronicity effect. Cross-sectional snapshots may capture transient, situational loneliness, whereas longitudinal cohorts may better identify entrenched or persistent social disconnection. This interpretation is consistent with longitudinal evidence indicating that persistent loneliness is particularly relevant to later stress and mental health outcomes [29].

7. Mechanisms: Immediate social pain vs. physical incubation

The disparity in magnitude between the mental ($r = 0.42$) and physical ($r = 0.19$) associations supports a cautious “dual-pathway” interpretation of loneliness in midlife.

The strong mental health correlation supports the evolutionary theory of loneliness as “social pain”. Subjective disconnection acts as an immediate alarm signal, manifesting rapidly as depression, anxiety, and perceived stress. The magnitude of this effect in midlife is comparable to that seen in older adults, indicating that the psychological anguish of isolation is age-invariant.

The moderate physical association (r = 0.19) likely reflects a broad physical health burden rather than a single biological endpoint.

Table 1
Characteristics of Included Studies.*

Study	Country	Design	N	Loneliness Measure	Mental Outcome	Physical Outcome
Greene et al. [15]	USA	Cross-sectional	401	UCLA-3	HSQ-12	HSQ-12
Sol et al. [16]	USA	Longitudinal	1407	Single Item	CES-D	Self-Rated Health
Sol et al. [16]	USA	Longitudinal	873	Single Item	CES-D	Self-Rated Health
Sol et al. [16]	USA	Longitudinal	570	Single Item	CES-D	Self-Rated Health
Crespo-Sanmiguel [17]	Spain	Cross-sectional	79	R-UCLA	WHOQOL	WHOQOL
Queen et al. [18]	USA	Longitudinal	968	HRS	CES-D	Self-Rated Health
Victor & Yang [19]	UK	Cross-sectional	1209	ESS	–	ESS Physical
Akeren & Akeren [20]	Turkey	Cross-sectional	611	LOS	Fear of Old Age	–
Luo & Li [21]	China	Longitudinal	7890	UCLA-3	CES-D	–
Kersten et al. [22]	Germany	Longitudinal	389	UCLA	Depression Scale	–
Toyoshima & Sato [23]	Japan	Cross-sectional	500	UCLA (J)	LSIK	–
Hansen et al. [24]	Norway	Cross-sectional	5574	Author Scale	SWLS	–
Klein et al. [25]	Germany	Cross-sectional	2513	TILS	Life Sat. Q	–
Nersesian et al. [8]	USA	Cross-sectional	927	MIDUS loneliness measure	–	IL-6, CRP
Tsai et al. [26]	Taiwan	Longitudinal	629	Author Scale	–	BP/Chronic Comp.
Lee et al. [27]	UK	Longitudinal	4211	R-UCLA	CES-D	–
Hawkley et al. [28]	USA	Longitudinal	229	R-UCLA	CES-D	Blood Pressure

* Note: Sol et al. locations inferred from cohort description; specific location NR in extraction. UCLA-3 = UCLA Loneliness Scale, three-item version; UCLA / UCLA (Japanese) = UCLA Loneliness Scale (standard / Japanese version); R-UCLA / UCLA-R = Revised UCLA Loneliness Scale; CES-D = Center for Epidemiologic Studies Depression Scale; WHOQOL = World Health Organization Quality of Life instrument; HSQ-12 = Health Status Questionnaire – 12 items; HRS = Health and Retirement Study loneliness measure; SRH = self-rated health; ESS = European Social Survey; LOS = Loneliness Orientation Scale; LSIK = Life Satisfaction Index K; SWLS = Satisfaction With Life Scale; TILS = Three-Item Loneliness Scale; MIDUS = Midlife in the United States; IL-6 = Interleukin-6; CRP = C-reactive protein; IADL = Instrumental Activities of Daily Living; BP = blood pressure; NR = not reported; USA = United States of America; UK = United Kingdom.

Table 2
Meta-Analytic Summary of Associations between Loneliness and HRQoL.

Outcome Domain	k	N (Total)	Model	Pooled r (95% CI)	*Z*-value	*p*-value	Heterogeneity (I^2)	Small-study effects (Egger's p)
Mental Health	14	21,777	Random	**0.42** (0.35, 0.49)	10.84	< 0.001	88.33%	0.001
Physical Health	10	7292	Random	**0.19** (0.12, 0.26)	5.49	< 0.001	84.88%	0.400

k, number of studies; CI, Confidence Interval; Random, Random-effects model.

Table 3
Moderator Analysis for Loneliness and HRQoL.

Outcome	Moderator	Level / Term (Ref. Noted)	Coef (z)	SE	Omnibus Q_M(df) p	R^2 Analog
Mental Health	Study Design	Longitudinal vs. Cross-sectional	0.81	0.14	32.85 (1), 0.001	0.81
	Gender Composition	Slope (% female)	0.10	0.04	8.15 (1), 0.004	0.51
	Marital Status	Slope (% married/partnered)	−0.01	0.01	1.41 (1), 0.235	0.00
Physical Health	Marital Status	Slope (% married/partnered)	0.04	0.02	4.86 (1), 0.028	0.55
	Gender Composition	Slope (% female)	−0.03	0.01	4.22 (1), 0.040	0.48
	Study Design	Longitudinal vs. Cross-sectional	0.09	0.21	0.19 (1), 0.665	0.00

Subjective physical health ratings, mobility or functional limitations, blood pressure, and inflammatory markers such as IL-6 and CRP reflect different levels of perception, function, and physiology. We pooled these outcomes because the available evidence base was small and because each indicator captures a physical dimension of health-related quality of life. Nevertheless, these constructs are not interchangeable. The physical health estimate should therefore be interpreted as a broad summary of the physical health burden, with future studies needed to more precisely separate subjective physical health, functional limitations, and biomarker pathways. As noted by Cole et al. [11], social regulation of gene expression can trigger immune dysfunction well before overt disease is visible.

Our moderator analyses highlight the possibility that subgroup and contextual factors shape the loneliness-health association. Gender composition significantly moderated both mental and physical outcomes, although the directions differed by domain and should be interpreted cautiously, as these analyses were based on study-level rather than individual-level data. Marital or partnership prevalence also moderated the association between loneliness and physical health, suggesting that relationship context may influence how loneliness translates into a physical health burden. This pattern is consistent with research on relationships showing that loneliness and relationship quality are dynamically linked over time [30].

8. Strengths and limitations

Strengths of this review include its pre-registered protocol (PROSPERO), rigorous effect-size standardisation, and specific focus on the midlife cohort. However, limitations must be acknowledged. First, substantial heterogeneity was observed (I2 > 80%), driven by diversity in populations, study designs, measurement instruments, and the pooling of subjective physical health indicators with objective biomarkers. This means that pooled estimates should be interpreted as average associations rather than precise universal effects. Second, the physical health domain combined constructs that may reflect different stages of the loneliness-health pathway, including perceived health, functional capacity, and physiological dysregulation. Third, evidence regarding small-study effects in the mental health analysis was mixed: Egger's test suggested funnel plot asymmetry, whereas trim-and-fill did not impute missing studies. This discrepancy may reflect substantial heterogeneity, differences in measurement precision, or genuine variation in effects rather than publication bias alone. Fourth, the review was restricted to English-language publications, which may have introduced language bias and may partly explain the limited geographic representation of the

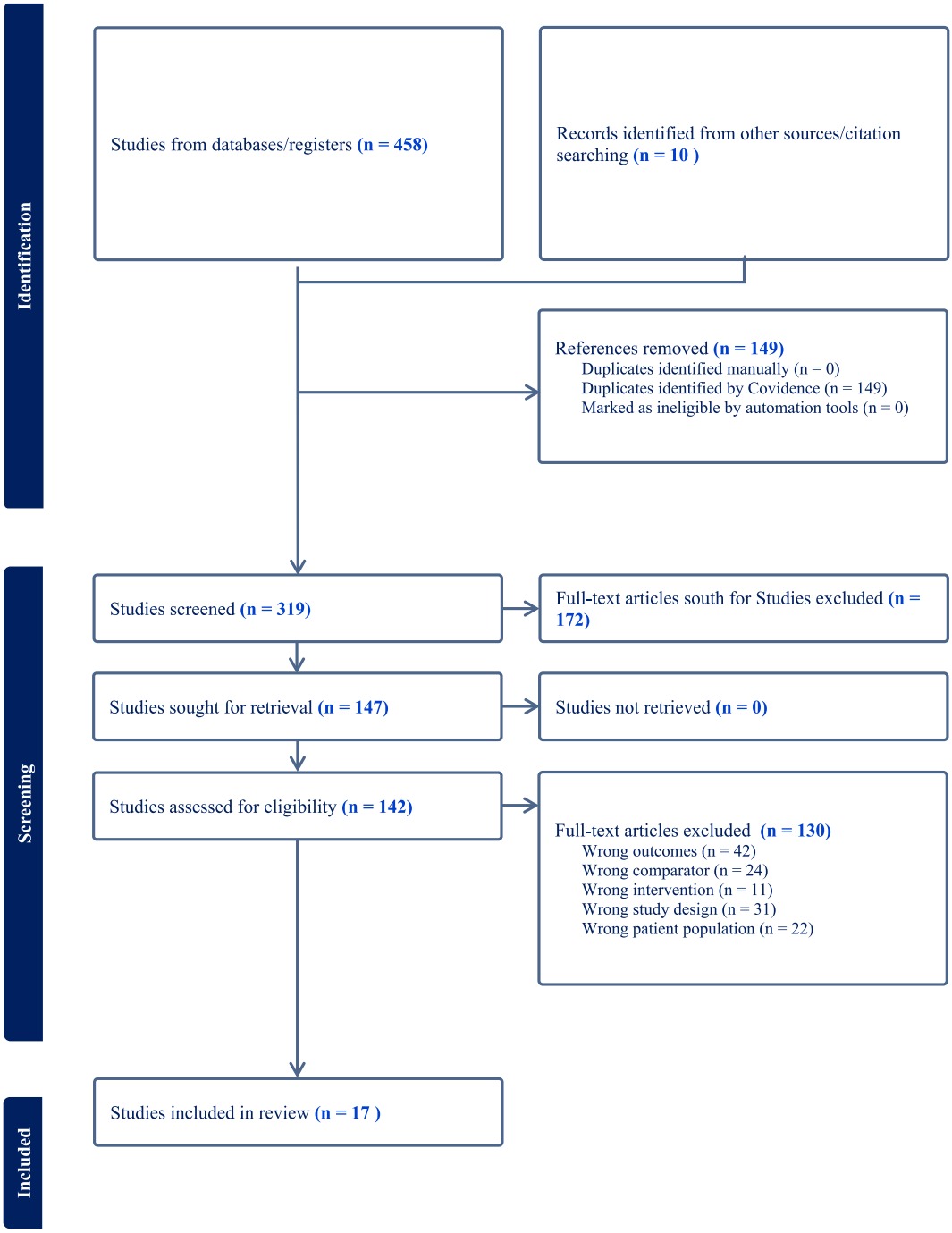

Fig. 1. PRISMA diagram for study selection.

evidence base. Finally, although longitudinal evidence was included, causal inference remains limited because observational studies are vulnerable to residual confounding and reverse causality.

9. Implications for policy and practice

Identifying loneliness as a midlife health risk has implications for prevention, but the clinical recommendations should be proportionate to the current evidence base. Current public health frameworks often prioritise loneliness in later life, whereas these findings suggest that adults aged 40–65 may also benefit from attention to social disconnection during routine psychosocial assessment. Assessment of loneliness may be considered within broader psychosocial risk evaluation, particularly during major midlife transitions such as divorce, bereavement, unemployment, caregiving strain, or emerging chronic illness. Interventions in this age group should prioritise evidence-informed approaches that address maladaptive social cognition, perceived stress, and opportunities for meaningful social connection before loneliness becomes chronic.

10. Conclusion

Loneliness is a significant correlate of health-related quality of life in middle adulthood. It is linked to an immediate burden on mental well-being and a smaller but meaningful burden on physical health. By characterising midlife as a potential period during which the health

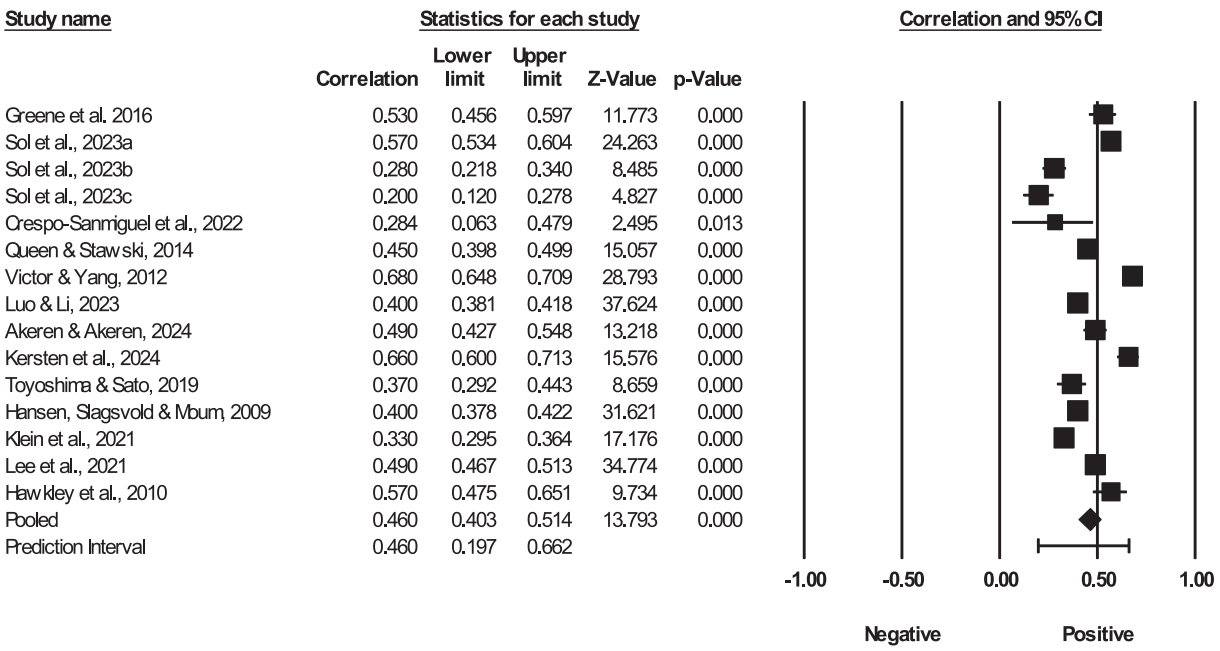

Fig. 2. Forest plot of the association between loneliness and mental health HRQoL (k = 14). The pooled correlation is $r = 0.42$ ($p < 0.001$).

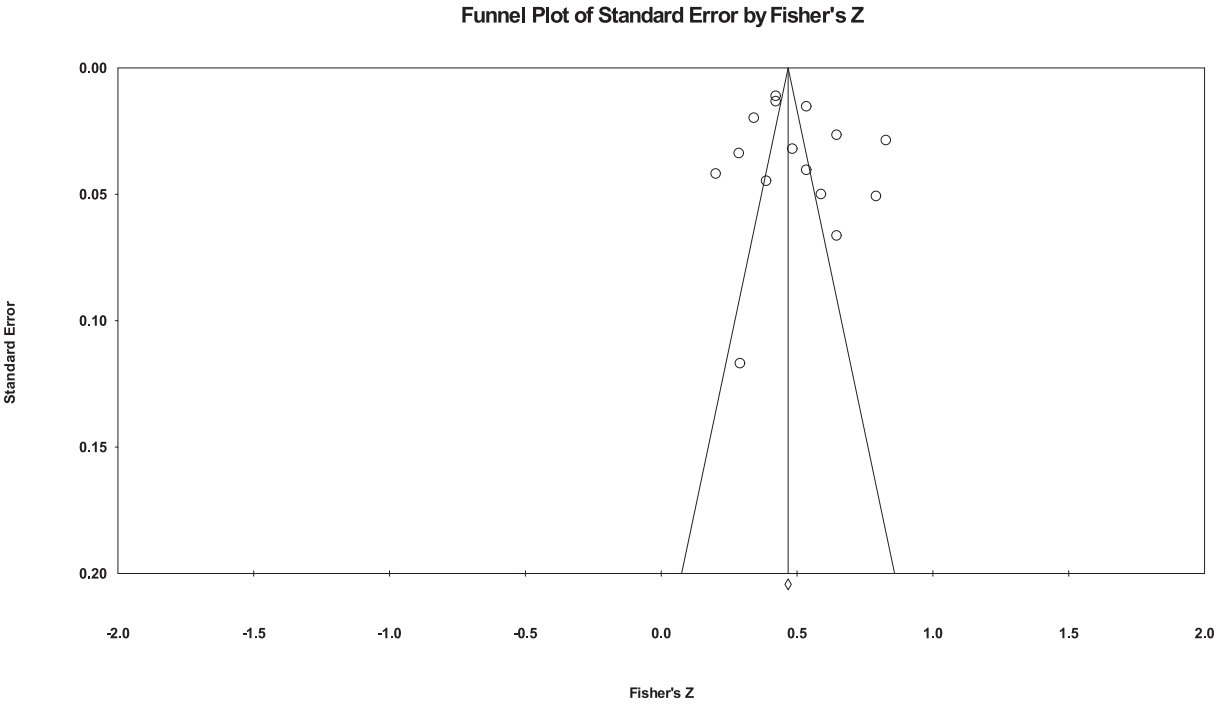

Fig. 3. Funnel plot of standard error by Fisher's Z for mental health studies.

costs of social disconnection begin to accumulate, this review highlights the value of earlier psychosocial assessment and intervention. Addressing loneliness in adults aged 40–65 may improve current well-being and may also contribute to healthier ageing trajectories, although stronger longitudinal and cross-cultural evidence is needed to clarify causal pathways and intervention targets.

Contributors

Lawrence E. Ugwu contributed to the conception and design of the review, search strategy, data extraction oversight, analysis, interpretation, and manuscript drafting.

Janine Anthea White and Tintswalo Mercy Hlungwani contributed to screening, data verification, interpretation of findings, and critical revision of the manuscript for important intellectual content.

All authors saw and approved the final version and no other person made a substantial contribution to the paper.

Informed consent

Informed consent was not applicable for this review as no direct contact with study participants occurred. All primary data were

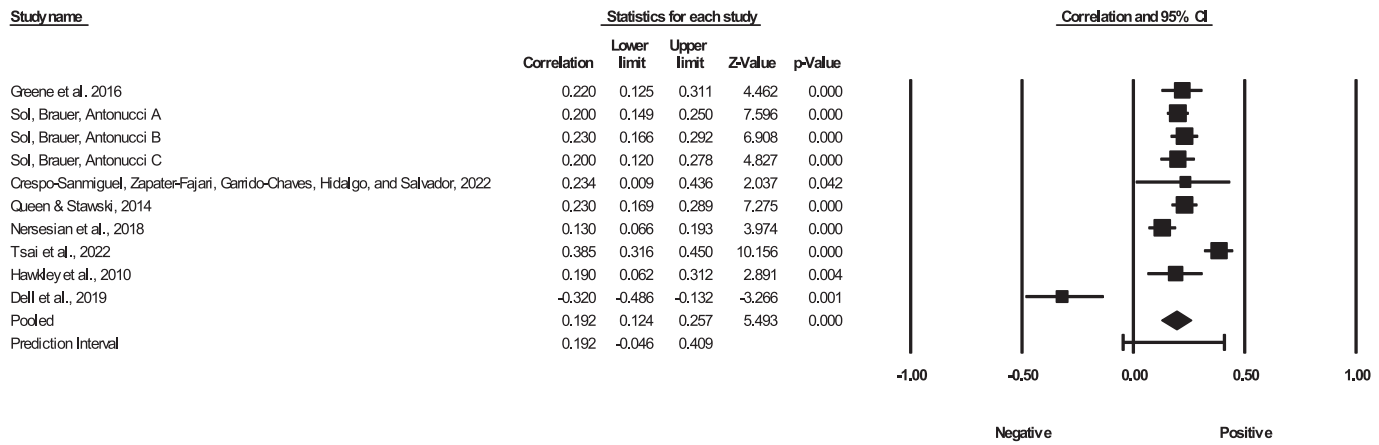

Fig. 4. Forest plot of the association between loneliness and physical health HRQoL (k = 10). The pooled correlation is r = 0.19 (p < 0.001).

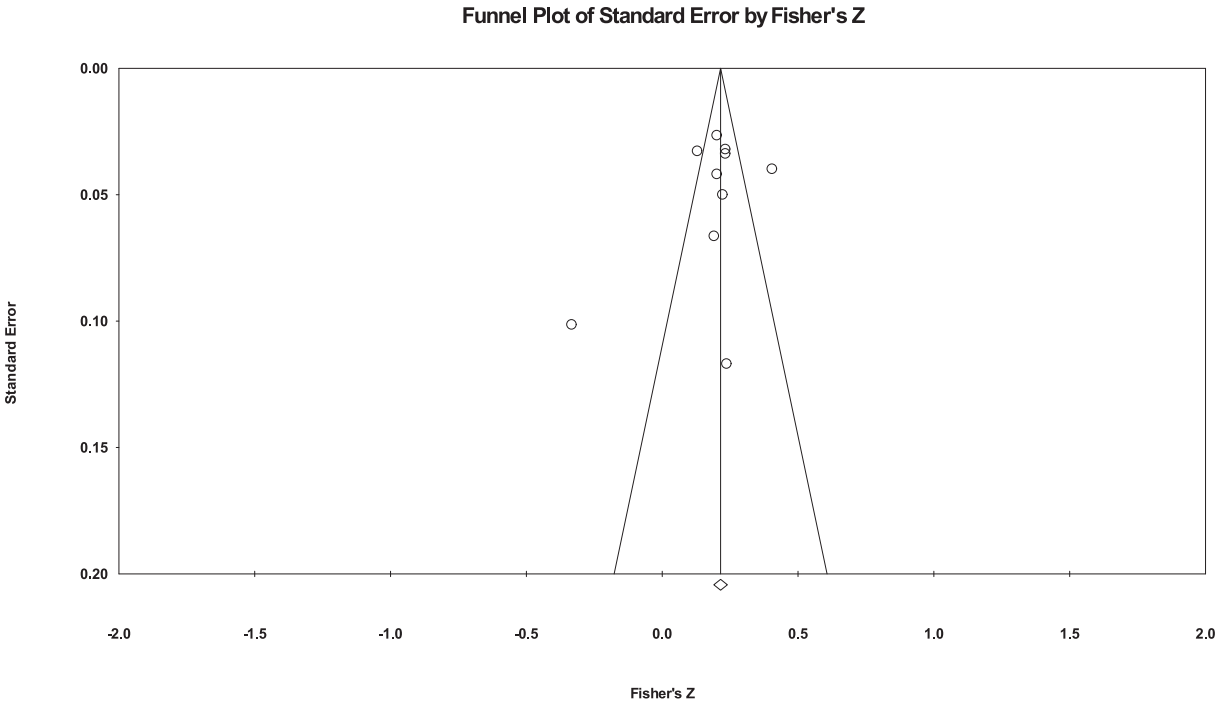

Fig. 5. Funnel plot of standard error by Fisher's Z for physical health studies.

anonymised and collected in the original independent studies, which were subject to their own respective ethical oversight and consent procedures.

Ethical approval

This study comprises a systematic review and meta-analysis of previously published observational studies. As the analysis relied exclusively on aggregated, secondary data retrieved from public biomedical databases and did not involve the recruitment of human participants or animals, formal ethical approval from an Institutional Review Board (IRB) or ethics committee was not required.

Study conduct and standards

The study was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol, including the analysis plan and moderator framework, was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420251016561.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

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Declaration of competing interest

The authors declare that they have no competing interest.

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