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Is Sensory Loss an Understudied Risk Factor for Frailty? A Systematic Review and Meta-analysis

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Abstract

Background

Age-related sensory loss and frailty are common conditions among older adults, but epidemiologic research on their possible links has been inconclusive. Clarifying this relationship is important because sensory loss may be a clinically relevant risk factor for frailty.

Methods

In this systematic review and meta-analysis, we searched 3 databases for observational studies investigating 4 sensory impairments—vision (VI), hearing (HI), smell (SI), and taste (TI)—and their relationships with frailty. We meta-analyzed the cross-sectional associations of VI/HI each with pre-frailty and frailty, investigated sources of heterogeneity using meta-regression and subgroup analyses, and assessed publication bias using Egger's test.

Results

We included 17 cross-sectional and 7 longitudinal studies in our review (N = 34,085) from 766 records. Our cross-sectional meta-analyses found that HI and VI were, respectively, associated with 1.5- to 2-fold greater odds of pre-frailty and 2.5- to 3-fold greater odds of frailty. Our results remained largely unchanged after subgroup analyses and meta-regression, though the association between HI and pre-frailty was no longer significant in 2 subgroups which lacked sufficient studies. We did not detect publication bias. Longitudinal studies largely found positive associations between VI/HI and frailty progression from baseline robustness, though they were inconclusive about frailty progression from baseline pre-frailty. Sparse literature and heterogenous methods precluded meta-analyses and conclusions on the SI/TI–frailty relationships.

Conclusions

Our meta-analyses demonstrate significant cross-sectional associations between VI/HI with pre-frailty and frailty. Our review also highlights knowledge gaps on the directionality and modifiability of these relationships and the impact of SI/TI and multiple sensory impairments on frailty.

Keywords

Gustatory deficit, Hearing loss, Olfactory dysfunction, Sensation disorders, Visual impairment

Though dismissed as a "normal" consequence of aging just 2 decades ago (1), frailty is now recognized as a syndrome of accelerated physiologic decline, distinct from comorbidity, disability, and aging (2), and which results in increased vulnerability to external stressors (3). Frailty is a major public health concern, especially among older adults aged ≥65 years in both Asian and Western populations, where over half are either pre-frail or frail (4,5). This places them at elevated risks of experiencing falls, disability, long-term care, and mortality (6). Crucially, frailty is also reversible given appropriate interventions (7,8). Hence, understanding the risk factors and underlying mechanisms for frailty is vital for informing novel strategies to prevent, delay, or reverse this condition.

Self-reported and objectively measured impairments of the sensory systems, including vision (VI), hearing (HI), smell (SI), and taste (TI), have been postulated as potential risk factors for frailty (9–14), due to their associations with established frailty risk factors [eg, physical inactivity (15), anorexia of aging (16,17), cognitive impairment (18), and depression (19,20)] and consequences of frailty [eg, falls (21), functional decline (22,23), and mortality (24)]. However, existing literature on the sensory impairment–frailty relationship is inconclusive (25,26) and is especially unclear about the uni- or bi-directionality of that relationship. Among older adults aged 57–85 years in the United States, the reported prevalence of VI, HI, SI, and TI are 20%, 18%, 22%, and 74% respectively, with 94% of older adults having at least 1 of these sensory impairments (27). Given how prevalent sensory impairments are, it is imperative to better understand how they may potentially contribute to frailty.

To address this gap, we conducted a systematic review and meta-analysis to examine the cross-sectional and longitudinal associations between various sensory impairments (VI, HI, SI, and TI) each with pre-frailty and frailty.

Methods

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our Supplementary Protocol is available online. Minor deviations are described below. Studies were retrieved and evaluated for their risk of bias by 1 author (B.K.J.T.) and independently verified by another (R.E.K.M.). If consensus could not be reached, 2 co-authors (A.T.L.G. and E.L.L.) were consulted for adjudication. Data extraction was performed by one author (B.K.J.T.) and vetted by 2 others (R.E.K.M. and A.T.L.G.).

Search Strategy

We searched 3 databases (PubMed, Embase, and the Cochrane Database of Systematic Reviews) from inception till 5 May 2020 using both free text and controlled vocabulary (MeSH or Emtree). Our core search comprised terms relating to the four types of sensory impairment covered in this review (vision, hearing, smell, or taste) AND "impairment" or 17 relevant synonyms, for example, "loss," "decline," "dysfunction," "poor," AND "frailty." To be comprehensive, we accounted for word variations and medical terms for each of the senses (eg, "visual," "sight," "eyesight," "seeing"; "audition," "aural," "olfactory," "gustatory") and single words that could replace "sensory impairment" ("blindness," "deafness," "anosmia," "hyposmia," "ageusia," "hypogeusia"). This continued until we reached a saturation point where additional terms yielded no new findings. We also hand-searched the bibliographies of included articles, as well as pertinent reviews and journals to identify 2 additional relevant records (28,29). Our full search strategy and PRISMA checklist are reported in Supplementary Methods 1 and 2.

Study Selection

We screened potentially eligible studies based on title and abstract, following which, we retrieved full texts for evaluation. Given that sensory loss may have been a minor component in some studies that investigated "correlates" or "geriatric syndromes" associated with frailty, we exercised caution for these ambiguous records and retrieved full texts for further evaluation.

Our inclusion criteria are:

1. Population: adults aged ≥55 years. We included participants in late middle age (55–64 years), in addition to older adults (≥65 years), since frailty is not an uncommon phenomenon in late middle age (30), and this increases the relevance of our findings to physicians and policymakers seeking to prevent frailty earlier in life.
2. Exposures: impairments of vision, hearing, smell, or taste; measured using objective (eg, Snellen chart, pure-tone audiometry, smell sticks, taste solutions of varying concentrations) or validated subjective assessments (eg, whisper test); as well as self-report.
3. Comparators: participants without sensory impairment as defined above.
4. Outcomes: prevalence, incidence, or progression of pre-frailty and frailty, defined based on original or modified versions of validated criteria. For example, the Fried frailty phenotype (6) defines pre-frailty as the presence of 1–2, and frailty as ≥3 of the following 5 criteria: unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. Some studies have modified this to suit practical requirements (13,28,29,31–34). Other definitions of frailty were also accepted, such as: the Canadian Study of Health and Aging-Clinical Frailty scale (CSHA-CFS) (35); Study of Osteoporotic Fractures (SOF) frailty criteria (36); Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight (FRAIL) Scale (37); and Health, Aging, and Body Composition (Health ABC) study frailty criteria (38).
5. Study type: observational studies (cross-sectional, longitudinal, and case–control) published as full-length articles or conference abstracts in peer-reviewed journals. No restrictions on language were applied and full texts in foreign languages, such as the study by Yang et al. (39), were translated by native speakers.

We excluded studies which:

1. Focused on specific subpopulations/special risk groups (eg, individuals with cardiovascular disease).
2. Included the presence of any of the sensory impairments in their definition of frailty.
3. Investigated disease-specific instead of sensory-specific associations (eg, cataract or glaucoma instead of VI).
4. Failed to distinguish between the different types of sensory impairments.

Data Extraction

We extracted the following data from each article: first author, year published, study design, setting, country, region, sample size, percentage male, mean/median age, type of sensory impairment, method of detecting impairment, frailty definition, adjustment for confounders, statistical methods, and key findings. We attempted contact with 18 corresponding authors to obtain additional unpublished information, such as participant characteristics, raw cell counts, and adjusted odds ratios (ORs) (10–12,14,28,29,31–34,39–46), of whom 9 authors responded (11,12,14,29,34,40–42,45,46).

Risk of Bias

We used the Newcastle-Ottawa Scale (NOS) (47), acknowledged by the Cochrane Collaboration (48), to evaluate the risk of bias at the outcome level. The 9-star NOS was originally designed to assess longitudinal and case–control studies and later adapted to a 10-star NOS for cross-sectional studies (49). As per the NOS grading in past reviews, we graded studies as having a high (<5 stars), moderate (5–7 stars), or low risk of bias (≥8 stars) (50,51).

Statistical Analysis

In the course of our systematic review, we found sufficient data in the literature to proceed with our planned meta-analyses on the cross-sectional relationships between VI or HI each with frailty, but not for SI or TI with frailty. We could not proceed with planned meta-analyses for any longitudinal relationships due to insufficient data. However, we included the baseline cross-sectional associations from longitudinal studies, if available, in our meta-analyses. We thus pooled the cross-sectional associations relating VI and HI to the odds of (i) pre-frailty and (ii) frailty. If more than 1 OR was available from the same study for a particular outcome due to multiple models and designs, we selected the OR that was maximally adjusted. Where studies omitted reporting an adjusted OR due to stated insignificance, and if the authors could not be contacted, we assumed a null OR and estimating standard errors from a univariable logistic regression analysis of frequency counts, as previously described by Nicholson et al. (52). If studies performed only a chi-squared test, or if their chosen effect estimate, exposure definition, or outcome definition was incompatible for synthesis with the majority of other studies (see Supplementary Table 1 footnotes), we calculated the unadjusted OR from the published or author-provided baseline frequency counts. We assessed and considered between-study heterogeneity as significant, if the p-value for the Q-test was <.10 or if the I2 statistic was ≥50% (53). Having observed substantial heterogeneity across all outcomes, we applied the random-effects model to synthesize study effects (54). To study potential sources of study heterogeneity, we performed univariable random-effects meta-regression analysis of various study-level characteristics: (i) frailty prevalence; (ii) age (% aged ≥75) and gender (% female); (iii) covariate adjustment (yes vs no); (iv) race (Asian vs Caucasian); (v) study design (cross-sectional vs longitudinal); (vi) risk of bias; (vii) frailty definition (Fried vs modified Fried or other criteria); (viii) measure of impairment (objective/validated, eg, Snellen/audiometry/whisper test vs self-report); and (ix) study setting (community vs hospital-based). Variables (v) and (ix) were later removed as only cross-sectional associations were meta-analyzed and there was only 1 hospital-based study. We repeated the meta-analyses in subgroups to explore the sensitivity of our results to the same study characteristics. Finally, we assessed funnel plot asymmetry both visually and using Egger's bias test (55,56). Where publication bias was suspected, we conducted a sensitivity analysis using the trim-and-fill method to re-estimate the pooled OR after imputing studies that were potentially missing (57). This method assumes that effect sizes are normally distributed around the centre of the funnel plot in the absence of publication bias (56).

We conducted all analyses using Stata, version 15.0. We considered a 2-sided p value <.05 as statistically significant for the purpose of these analyses.

Results

We screened the titles and abstracts of 766 non-duplicated records, of which, we retrieved and examined 79 full-text articles (PRISMA flow diagram; Figure 1). In total, we included 24 studies in our systematic review and 18 in our meta-analyses. With some overlap, 15 studies investigated VI (11,14,28,29,31,33,34,39–41,43–46,58), 16 investigated HI (10,12,28,29,31–34,40–45,59,60), 3 investigated SI (9,13,61), and 2 investigated TI (9,13).

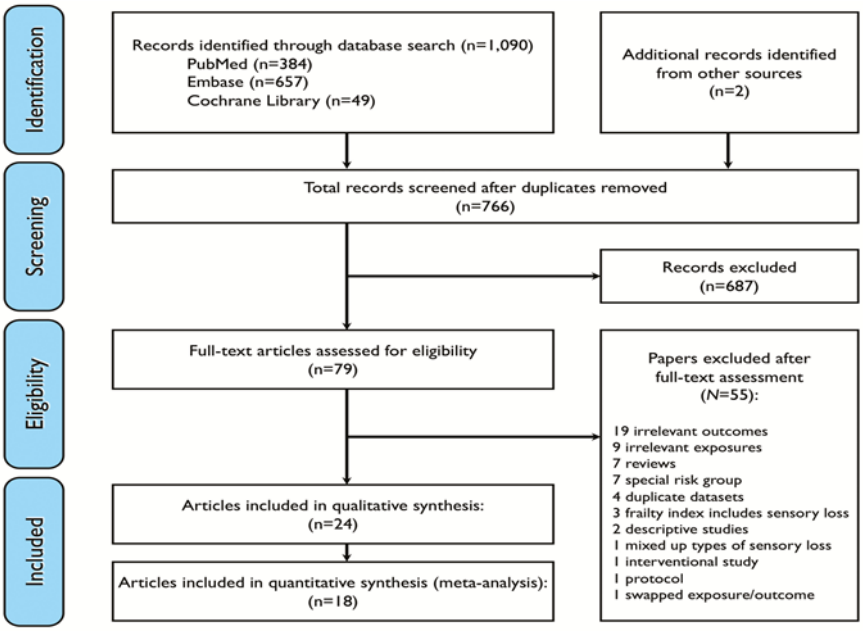

Fig. 1. PRISMA flow diagram showing the study selection process

Study Characteristics

Study characteristics are summarized in Supplementary Table 1. Briefly, there were 17 cross-sectional and 7 longitudinal studies, with a total of 34,085 participants. There were no case–control studies. Follow-up duration for the longitudinal studies ranged from 1 to 10 years. Sample sizes ranged from 141 to 4,026. All were population-based studies, except 1 which recruited 1,126 participants from hospital outpatient clinics (43). Ten studies drew from Asian populations and 13 from Caucasian populations. One other study included both Asian (25%) and Caucasian (75%) individuals from 5 countries and was regarded as a Caucasian majority population during meta-regression analyses (44). All studies included in our meta-analyses had a moderate (NOS 5–7) or low (NOS ≥ 8) risk of bias at both the outcome and study level.

Measurement of Frailty

Nine studies (11,14,40,41,43–46,61) defined frailty according to the Fried frailty phenotype (6), and another 10 studies each modified the Fried criteria (13,28,29,31–34,58,60). We synthesized these together in our meta-analyses and explored the differences in pooled ORs via subgroup analyses. Four additional studies (9,10,39,42) each used different criteria: CSHA-CFS (35), SOF frailty criteria (36), FRAIL Scale (37), and Health ABC frailty criteria (38). We made a post hoc decision to exclude these 4 definitions from meta-analyses because their agreement with the Fried criteria has been shown to be insufficient (62).

Vision Impairment

Measurement of VI

Sixteen studies (11 cross-sectional and 5 longitudinal, comprising 23,115 total participants) investigated the relationship between VI and frailty outcomes (Supplementary Table 1). Four longitudinal studies also reported baseline cross-sectional associations (11,14,39,45). Seven studies measured VI objectively. Among these 7 studies, VI was varyingly defined as: distance visual acuity worse than 20/40 (0.3 LogMar) in 4 studies (reported in 3 articles) (14,33,46), distance visual acuity worse than 20/50 (0.4 LogMar) in 1 study (45), and near visual acuity worse than 20/40 (0.3 LogMar) in 2 studies (41,58). The remaining 9 studies measured VI by self-report (11,28,29,31,34,39,40,43,44).

Cross-sectional associations

Among the 15 cross-sectional associations reported on VI and frailty outcomes, 2 studies from the same study population (National Health and Nutrition Examination Survey 1999–2002; NHANES) separately reported the relationships between impairments in distance visual acuity or near visual acuity with frailty (14,58); to avoid double counting, we included only the former in meta-analyses. We excluded 1 other study from meta-analyses due to insufficient data (40), and another due to incompatible frailty criteria (39).

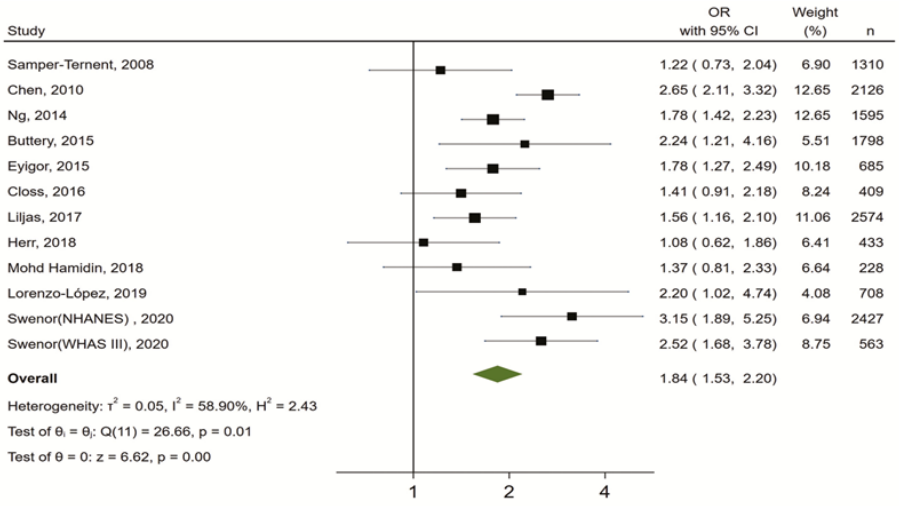

Fig. 2. Random-effects meta-analyses of the cross-sectional association between vision impairment and pre-frailty. The diamond represents the estimated pooled odds ratio (OR) for each meta-analysis; box sizes reflect the relative weight apportioned to studies in the meta-analysis. N = 14,856.

Meta-analyses.

Of the 12 studies which examined the cross-sectional association between VI and pre-frailty, 8 studies (reported in 7 articles) found a significant association (11,14,28,31,33,43,45), while 4 studies did not find any association (29,41,44,46). Pooling these estimates (Figure 2), we found that VI was associated with approximately 2-fold higher odds of pre-frailty (pooled OR = 1.84, 95% CI = 1.53–2.20, p < .001, I2 = 58.9%, N = 14,856).

Among the 12 studies which examined the cross-sectional association between VI and frailty, 9 studies (reported in 8 articles) found a significant association (11,14,28,31,33,41,44,45), 2 studies found a borderline significant association (p = .05) (29,46), and 1 study did not find any association (43). Pooling these estimates (Figure 3), we found that VI was associated with 3-fold higher odds of frailty (pooled OR = 3.16, 95% CI = 2.27–4.40, p < .001, I^2 = 66.3%, N = 10,095).

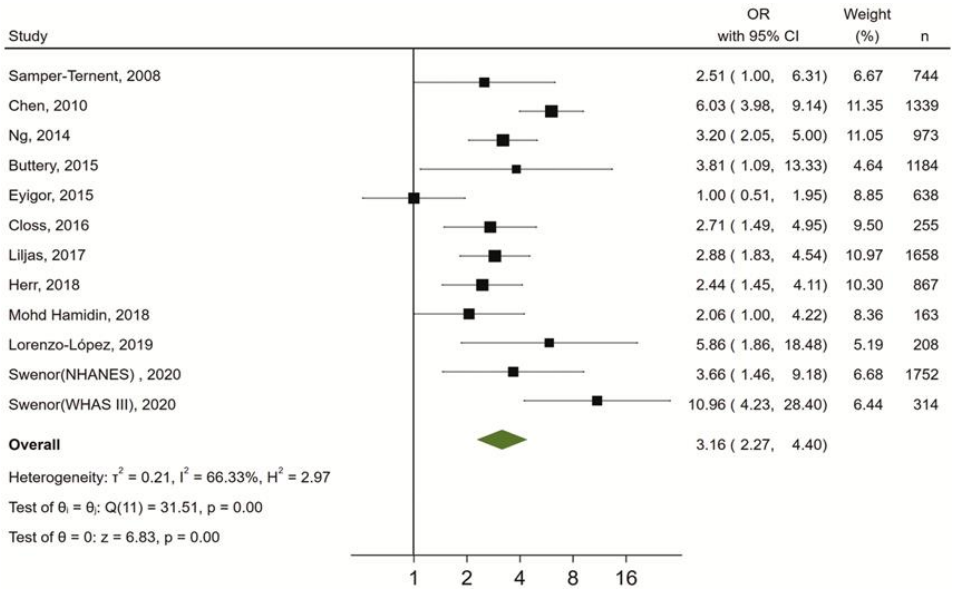

Fig. 3 Random-effects meta-analyses of the cross-sectional association between vision impairment and frailty. The diamond represents the estimated pooled odds ratio (OR) for each meta-analysis; box sizes reflect the relative weight apportioned to studies in the meta-analysis. N = 10,095.

Subgroup analyses, meta-regression, and publication bias.

Subgroup analyses stratified by categorical study-level characteristics are reported in Supplementary Table 2. These characteristics include: adjustment for confounders (yes vs no), race (Asian vs Caucasian), risk of bias (NOS < 8 vs NOS ≥ 8), frailty criteria (Fried vs modified Fried), and measurement of VI (objectively rated vs self-reported). Pooled associations remained significant across all subgroups. Meta-regression of these same categorical characteristics (Supplementary Table 3) showed that they did not significantly modify effect sizes, apart from 1 instance where the pooled odds of pre-frailty was significantly smaller (though still positive) among studies using Fried criteria than studies using modified Fried criteria. Meta-regression of continuous study-level characteristics (Supplementary Table 3) did not suggest that age, gender, and frailty prevalence were significant effect modifiers. An additional sensitivity analysis showed that our decision to include the study by Closs et al. (41) (which measured near rather than distance visual acuity) had no appreciable impact on the pooled ORs. Egger's bias test did not detect funnel plot asymmetry in either meta-analysis (Supplementary Table 4), thus we did not follow-up with the trim-and-fill method.

Additional meta-analyses.

For completeness, we further meta-analyzed the cross-sectional associations between (i) VI and frailty (vs pre-frailty), and (ii) VI and any frailty (ie, combined pre-frailty/frailty) as per our protocol. Findings were similar, with pooled estimates (Supplementary Figures 1 and 2) showing approximately 2-fold higher odds for both associations. The accompanying subgroup, meta-regression, and publication bias analyses are available in Supplementary Tables 2–4. As these additional analyses do not substantially alter our conclusions, we will not discuss them further.

Longitudinal associations

Five studies investigated the multivariable-adjusted longitudinal associations between VI and frailty outcomes (Supplementary Table 1), with all except 1 study (specified below) using the Fried or modified Fried criteria to define frailty. However, their varying analytical methods precluded a meta-analysis.

Among baseline robust participants, longitudinal studies mostly found that VI was a risk factor for frailty progression. Specifically, Liljas et al. (11) and Trevisan et al. (34), respectively, reported 1.86-fold (95% CI = 1.17–2.95, N = 698, 4 years) and 1.37-fold (95% CI = 1.24–1.49, N = 1,261, 4.4 years) higher incident odds of any frailty among baseline robust participants with self-reported VI. Similarly, Swenor et al. (14) reported higher odds of incident frailty at 3-year follow-up among baseline robust participants (N = 549) with moderate-to-severe objectively measured VI (OR = 3.5, 95% CI = 1.4–8.4), but not participants with only mild VI (OR = 2.2, 95% CI = 0.9–5.4).

Among baseline pre-frail participants, longitudinal studies reported conflicting findings. Trevisan et al. (34) found that baseline pre-frail participants with self-reported VI had a significantly higher odds of incident frailty (OR = 1.18, 95% CI = 1.05–1.33, N = 1,441) at 4.4-year follow-up. Conversely, Liljas et al. (11) did not find any association at 4-year follow-up (OR = 1.34, 95% CI = 0.82–2.19, N = 1,178).

Two other studies require separate consideration. Lorenzo-Lopez et al. (45) reported that among participants with objectively measured VI, there was no significant difference between the number of deteriorations or improvements in frailty status at 1-year follow-up (p-value not reported, N = 749). Conversely, Yang et al. (39) reported 2-fold higher odds of any worsening of frailty status (FRAIL scale) among participants with self-reported VI at baseline (OR = 2.02, 95% CI = 1.27–3.22, N = 507, 3 years). We note that these studies had assumed 1-stage transitions (eg, robust to pre-frail, or pre-frail to frail) and 2-stage transitions (eg, robust to frail, or vice versa) to be equivalent when counting the number of deteriorations or improvements in frailty, though they did not provide further justification for this assumption.

Hearing Impairment

Measurement of HI

Sixteen studies (11 cross-sectional and 5 longitudinal, comprising a total of 24,124 participants) investigated the relationship between HI and frailty outcomes (Supplementary Table 1). Four longitudinal studies also reported baseline cross-sectional associations (10,12,42,45). Six studies utilized objective assessments of HI: Kamil et al. (10) measured HI using pure-tone audiometry at 0.5, 1, 2, and 4 kHz, and defined 26–40 dB and >40 dB as the cutoffs for mild and moderate-or-greater HI respectively; Doba et al. (42) recorded continuous pure-tone audiometric measurements at 2 and 4 kHz, as well as self-reported HI; 4 other studies (33,40,41,45) used the validated whisper test, where participants were considered to have HI if they could not repeat ≥3 out of a possible total of 6 letters/numbers correctly, whispered at a distance of 0.6 m behind the participant's field of vision (63). The remaining 10 studies relied on self-reported HI (12,28,29,31,32,34,43,44,59,60).

Cross-sectional associations

Among the 15 cross-sectional associations reported on HI and frailty outcomes, 2 studies reported insufficient data for inclusion in meta-analyses (40,60), and 2 studies used incompatible frailty criteria (10,42). One other study could only be included in 1 meta-analysis (HI and odds of any frailty; Supplementary Figure 4) as it did not report sufficient data for other meta-analyses (32).

Meta-analyses.

Among the 10 studies investigating the cross-sectional association between HI and pre-frailty, 5 studies (11,28,33,43,44) found positive associations while 5 did not find an association (29,31,41,45,59). Pooling these estimates (Figure 4), we found that HI was associated with 1.5-fold higher odds of pre-frailty (pooled OR = 1.61, 95% CI = 1.28–2.01, $p < .001$, $I^2 = 65.2\%$, N = 14,329).

Among the 10 studies investigating the cross-sectional association between HI and frailty, 7 found positive associations (12,28,29,31,41,43,44), while 3 did not find an association (33,45,59). Pooling these estimates (Figure 5), we found that HI was associated with 2.5-fold higher odds of frailty (pooled OR = 2.53, 95% CI = 1.88–3.41, $p < .001$, I2 = 53.4%, N = 9,322).

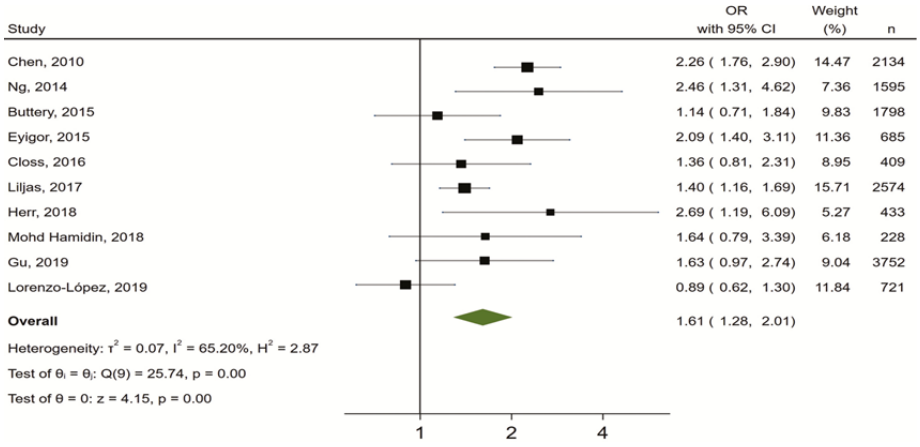

Fig. 4. Random-effects meta-analyses of the cross-sectional association between hearing impairment and pre-frailty. The diamond represents the estimated pooled odds ratio (OR) for each meta-analysis; box sizes reflect the relative weight apportioned to studies in the meta-analysis. N = 14,329.

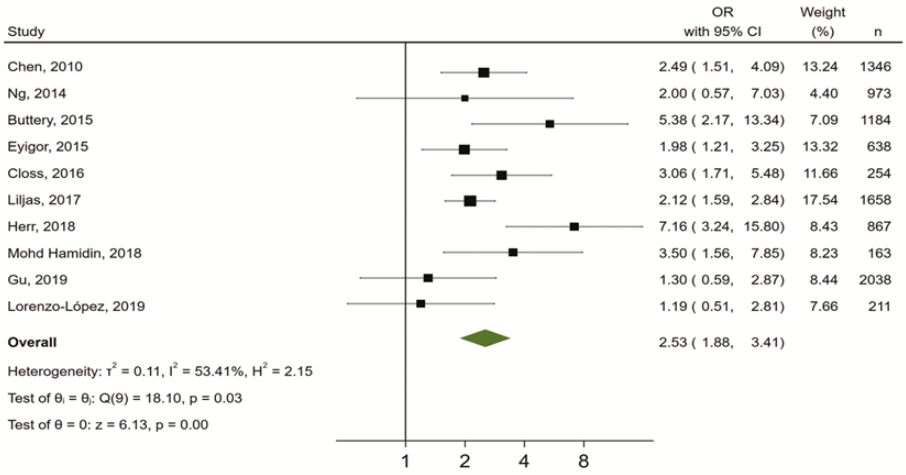

Fig. 5 Random-effects meta-analyses of the cross-sectional association between hearing impairment and frailty. The diamond represents the estimated pooled odds ratio (OR) for each meta-analysis; box sizes reflect the relative weight apportioned to studies in the meta-analysis. N = 9,332

Subgroup analyses, meta-regression, and publication bias.

Subgroup analyses stratified by categorical study-level characteristics are reported in Supplementary Table 2. In 2 subgroups, the pooled association of HI with pre-frailty became nonsignificant: covariate-adjusted subgroup (pooled OR = 1.34, 95% CI = 0.94–1.91, p = .101, I2 = 0.0) and objective HI measurement subgroup (pooled OR = 1.38, 95% CI = 0.78–2.43, p = .267, I2 = 54.2). We note that both these subgroups had very few constituent studies (2 and 3 studies, respectively). Pooled associations remained significant in other subgroups. Meta-regression of these same categorical characteristics (Supplementary Table 3) did not find significant effect modifiers, apart from 1 instance where the pooled odds of pre-frailty was significantly lower (though still positive) among studies of Caucasian populations than studies of Asian populations. Meta-regression of continuous study-level characteristics (Supplementary Table 3) did not find that age, gender, and frailty prevalence were significant effect modifiers. Egger's bias test did not detect funnel plot asymmetry in either meta-analysis (Supplementary Table 4), thus we did not follow-up with the trim-and-fill method.

Additional meta-analyses.

For completeness, we further meta-analyzed the cross-sectional associations between (i) HI and frailty (vs pre-frailty), and (ii) HI and any frailty (ie, combined pre-frailty/frailty) as per our protocol. Findings were similar, with pooled estimates (Supplementary Figures 3 and 4) showing approximately 2-fold higher odds for both associations. The accompanying subgroup, meta-regression, and publication bias analyses are available in Supplementary Tables 2–4. As these additional analyses do not substantially alter our conclusions, we will not discuss them further.

Longitudinal associations

Five studies investigated the multivariable-adjusted longitudinal associations between HI and frailty outcomes (Supplementary Table 1), with all except 2 studies (specified below) using the Fried or modified Fried criteria to define frailty. However, their varying analytical methods precluded a meta-analysis.

Among baseline robust participants, longitudinal studies mostly found that HI was a risk factor for frailty progression. Specifically, Kamil et al. reported a higher incident risk of frailty (measured by Health ABC criteria) among baseline robust participants (N = 1,965) with moderate-or-greater HI (measured with audiometry; HR = 1.63, 95% CI = 1.26–2.12, 10 years), but not among participants with mild HI (HR = 1.12, 95% CI = 0.90–1.39, 10 years). Baseline HI analyzed as a continuous variable was also associated with incident frailty (HR = 1.11, 95% CI = 1.03–1.10). Similarly, among baseline robust participants with self-reported HI, Doba et al. (42) reported 2.19-fold (95% CI = 1.20–4.00, N = 246, 5 years) higher incident odds of frailty (measured by the CSHA-CFS), and Trevisan et al. (34) found 1.13-fold (95% CI = 1.03–1.23, N = 1,261, 4.4 years) higher incident odds of any frailty. Conversely, Liljas et al. (12) did not find any association between self-reported HI and incident any frailty (OR = 1.32, 95% CI = 0.96–1.61, N = 1,396, 4 years).

Among baseline pre-frail participants, longitudinal studies reported conflicting findings. Liljas et al. (11) found that baseline pre-frail participants with self-reported HI had a significantly higher odds of incident frailty (OR = 1.57, 95% CI = 1.01–2.44, N = 1,178, 4 years). Conversely, Trevisan et al. (34) did not find any association (OR = 1.05, 95% CI = 0.93–1.20, N = 1,441, 4.4 years).

Finally, Lorenzo-Lopez et al. (45) reported that baseline HI (measured by the whisper test) was associated with more deteriorations than improvements in frailty status at 1-year follow-up (OR = 3.18, 1.08–9.39, N = 749). They assumed that 1-stage and 2-stage transitions are equivalent.

Smell Impairment and Frailty

Only 3 studies, all cross-sectional, investigated the relationship between SI and frailty (Supplementary Table 1) (9,13,61) and results were inconclusive. For example, Laudisio et al. (61) found a positive association between SI and frailty outcomes in an Italian population (odds of frailty: adjusted OR = 2.60, 95% CI = 1.39–4.85; odds of pre-frailty: adjusted OR = 1.59, 95% CI = 1.17–2.16; N = 1,035; multinomial logistic regression with robustness as the reference), while Somekawa et al. (13) did not find any association in a Japanese population (odds of frailty: adjusted OR = 1.73, 95% CI = 0.83–3.63, p = .15, N = 768; vs pre-frailty + robustness). The latter study (13) did, however, find a significant association of SI with the frailty criterion slow walking speed (OR = 2.46, 95% CI = 1.21–5.03, N = 768). Both studies measured SI subjectively using questionnaires. In contrast, Harita et al. (9) measured SI objectively using smell cards, where SI was defined as the correct recognition of ≤7 out of a maximum of 12 smells typically familiar to Japanese people. They found a significant association between SI and any frailty (adjusted OR = 2.25, 95% CI = 1.01–5.03, p = .048, N = 141), adjusted for age, sex, heart disease, digestive disease, bone/joint disease, body mass index, body fat mass index, and body mineral index, although this association was eliminated upon further adjustment for body protein index (adjusted OR = 2.07, 95% CI = 0.92–4.66, p = .079).

Taste Impairment and Frailty

Only 2 cross-sectional studies investigated the relationship between TI and frailty (Supplementary Table 1). Somekawa et al. (13) measured TI using a self-reported questionnaire and found a significant association with frailty (adjusted OR = 2.81, 95% CI = 1.29–6.12, p = .01, N = 768). In contrast, Harita et al. (9) found no significant difference in objectively assessed sweet and salty gustatory abilities (ability to recognize aqueous solutions of ≤0.25 g/% sodium chloride and ≤2 g/% sucrose respectively in a 1 mL whole mouth gustatory test) between robust, pre-frail and frail groups.

Discussion

In our systematic review and cross-sectional meta-analyses, we found overall that the presence of HI or VI was each significantly associated with a 1.5- to 2-fold greater odds of pre-frailty and 2.5- to 3-fold greater odds of frailty, respectively. The evidence from longitudinal studies further suggests that both VI and HI increase the odds of frailty progression from baseline robustness, although methodological variations between the different studies did not permit us to conduct a meta-analysis. In contrast to the ample literature on VI and HI, there were too few studies on SI, TI, and frailty to draw substantive conclusions or to proceed with our planned meta-analyses, with the handful of included studies reporting heterogenous methods and inconsistent findings. Hence, more observational studies are warranted to further investigate SI and TI as potential frailty risk factors.

Our findings raise queries on the possible causal link between VI/HI and frailty (Supplementary Figure 5), which may be explained by several pathways. First, fear of falling among older adults with eye diseases, such as glaucoma and age-related macular degeneration (64), is associated with avoidance of physical activity, which may dramatically speed up frailty progression (65). Second, the visually impaired are more likely to be lonely and socially isolated (65–67). Loneliness may increase the risk of physical inactivity, either because lonely older adults are less likely to participate in group activities, or because their poorer emotional self-regulation diminishes their motivation to engage in physical activity (68). Social isolation may also diminish diet quality, due to the absence of motivating factors and economies of scale from food procurement and preparation in social settings (69,70). Together, inactivity and malnutrition accelerate frailty (38,71). Other potential mediators between VI and frailty include cognitive impairment and depression, both of which have been established as long-term consequences of VI (64,72,73), and are also known frailty risk factors (74,75), The possible causal link between HI and frailty may similarly be explained by social isolation, cognitive impairment, and depression (18,76,77). Given these shared pathways of VI and HI with frailty, further research is needed to evaluate the impact of concomitant vision and hearing loss (ie, dual sensory loss) on frailty—a knowledge gap in existing literature.

Though a causal link between VI/HI and frailty is possible, we must also consider the likelihood that VI/HI are simply early physiological markers of clinically detectable frailty. This is because VI, HI, and frailty may all result from shared underlying pathologic processes (Supplementary Figure 5). For example, hypertension, diabetes mellitus, stroke, systemic inflammation, and neurodegenerative disease are 5 well-known risk factors for various ocular diseases contributing to VI (eg, cataract, glaucoma, diabetic retinopathy) (78–82), as well as otologic diseases contributing to HI (eg, sensorineural or central auditory dysfunction) (83–87). The same 5 conditions are also risk factors for frailty (74,88,89). We note, however, that many of the included studies had adjusted for these conditions as covariates (10–12,32–34), thus the measured associations may not be fully explained by the early marker hypothesis alone. A third plausible hypothesis is reverse causality (Supplementary Figure 5), where frailty increases the risk of VI and HI. This may be functional, in that frail persons may face greater barriers to seeking treatment or prioritizing care for their sensory impairments, or biologic, in that frailty is a known risk factor for incident Alzheimer's disease (90), which in turn disrupts complex visual functions and central auditory processing (82,87). In our review, we found that longitudinal studies evaluating the role of shared pathology and reverse causality in the VI– and HI–frailty relationship were lacking. Hence, there remains a need for comprehensive experimental studies, animal models, and longitudinal studies to better understand these processes. If frailty and sensory loss indeed share common underlying pathology and reverse causality, it may support the call for greater recognition of "sensory frailty" as a phenotype (25,26), alongside cognitive, social, and psychological frailty (91,92).

Having shown that VI and HI are risk factors for frailty, the corollary for physicians and policymakers is whether these risk relationships are amenable to intervention. Few intervention studies have been designed specifically to evaluate frailty as an outcome—we found only 1 in our systematic search, which reported that more than half of frail individuals reversed to a state of pre-frailty 1 month after cataract surgery (93). We can, however, infer that these risks are likely modifiable, given that even simple interventions such as spectacles or hearing aids have been shown to confer a significant mortality benefit in multivariate analyses (94). Nonetheless, randomized controlled trials and real-world prospective studies are required for firm conclusions and should be designed specifically with frailty as an outcome.

Finally, smell and taste are often overlooked as they are not considered essential for life (95). This is evident in the scant literature on their relationship with frailty, since we found only 3 studies on SI and 2 studies on TI, with conflicting results. However, these impairments warrant attention because they contribute to the anorexia of aging (16), a term that describes the decrease in appetite/food intake in old age which, in turn, is a modifiable risk factor for frailty, sarcopenia and mortality (96). Given also that TI and SI are also highly prevalent (74% and 22%, respectively, in American adults aged 57–85 years) (27), and that most older adults are unaware of their gradual decline (95), we recommend that future studies investigate these impairments as potential risk factors and intervention targets for frailty. However, in doing so, investigators should be aware that subjective measurements of smell and taste are especially susceptible to biases. In previous studies, participants tended to conflate smell and taste by reporting TI when they actually had SI (97), thus significantly underestimating the true prevalence of SI as determined by objective olfactory tests (98). This may explain the conflicting findings in our systematic review, where Somekawa et al. (13), who assessed SI and TI by self-report, found an association of frailty with TI but not SI, while Harita et al. (9), who measured both senses objectively, found that the reverse was true. Therefore, we recommend that future studies measure SI and TI objectively.

Strengths and Limitations

The strengths of our study lie in the large number of systematically included studies, from a diverse range of ethnicities, which make our findings generalizable to the target population of older adults. Our meta-regression and subgroup analyses did not substantially alter our findings and we found no evidence of publication bias.

Nonetheless, our study has several limitations. First, about half the included studies in our meta-analyses had modified the original Fried frailty phenotype, which may have influenced the quality of the composite score. Their modifications, however, were modest, as they had used proxy measurements of the same 5 criteria, without removing or adding criteria. Since modified Fried criteria have been shown to still have substantial reliability (Cohen kappa .68) as compared to the original Fried criteria (62), we synthesized these together and performed subgroup analyses. As all the Fried and modified Fried subgroups still showed positive associations of VI/HI with pre-frailty/frailty, and meta-regression identified frailty definition as a significant effect modifier in only 1 of 8 meta-analyses (VI and pre-frailty), our findings appear consistent irrespective of the frailty criteria used. Second, more than half the included studies relied on self-reported VI or HI, which may be subject to social desirability or recall bias; third, we included unadjusted estimates in the meta-analysis, which may introduce bias from unaccounted confounding. However, we found in subgroup analyses that nearly all associations remained positive in both the self-reported and objectively assessed impairment subgroups, as well as in the covariate-adjusted and unadjusted subgroups, suggesting that the positive findings are not entirely driven by any 1 subgroup. Nonetheless, we note that some subgroups may have limited power to detect associations and should be interpreted with caution. Specifically, the association between HI and pre-frailty was eliminated in 2 subgroups (objectively measured HI; covariate-adjusted), but as these subgroups contained only 2–3 studies for this association, future studies are required and may confirm or refute the association. Fourth, we could not consider severe frailty nor VI/HI severity in our subgroup analyses, as only 1–2 included studies had the relevant data. Fifth, we encountered moderate to high heterogeneity, which was only partially explained by our meta-regression analyses, indicating that other unknown sources of heterogeneity were present and may potentially have introduced bias in our findings. Finally, though impairments of balance (comprising vestibular, visual, and proprioceptive senses) and the general senses (touch, pressure, pain, temperature, etc.) are important, we did not consider them in this review, as they are composite senses with a complex range of pathology that require separate consideration.

Conclusion

Our meta-analyses demonstrate clear cross-sectional associations of VI and HI with pre-frailty and frailty. Longitudinal studies included in our systematic review further suggest that VI and HI are risk factors for frailty progression from baseline robustness. However, the precise mechanisms behind these epidemiologic associations are unclear and warrant further scrutiny. There is also a paucity of data on the cumulative risk of frailty in individuals with dual/multi-sensory loss. More importantly, randomized controlled trials and carefully designed real-world studies examining the impact of VI and HI interventions on frailty prevention are needed before we can recommend VI and HI treatment as a routine component of frailty prevention programs. Nevertheless, even if VI and HI are not causal factors for frailty, our results have at least established them as possible early physiological markers for frailty. As such, clinicians and policymakers should consider adding VI and HI screening to frailty detection programs. Finally, SI and TI should be investigated further as potential risk factors for frailty, as the current literature is too sparse to draw substantive conclusions. Our findings are an important contribution to the management of frailty in older adults and emphasize sensory loss as an important new dimension in managing this multifaceted syndrome.

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Conflict of Interest

V.V., B.K.S., C.T., L.L.-L., J.C.M.-C., C.H.A.S., A.L., S.A.S., and Y.T. are the authors of studies included in this systematic review and meta-analysis; however, they were not involved in grading the risk of bias, which was independently performed by B.K.J.T. and R.E.K.M. The other authors declare no conflicts of interest.

Author Contributions

B.K.J.T., R.E.K.M., A.T.L.G., and E.L.L. conceptualized and designed the study. B.K.J.T. and R.E.K.M. retrieved and evaluated records for risk of bias. B.K.J.T. extracted data from included articles and this was verified by R.E.K.M. and A.T.L.G. V.V., B.K.S., C.T., L.L.-L., C.H.A.S., A.L., and S.A.S. contributed data to the meta-analyses. A.T.L.G. performed the statistical analyses, which were verified by B.K.J.T. and R.E.K.M. B.K.J.T., R.E.K.M., and A.T.L.G. drafted the manuscript, which was critically revised by all authors, with substantial intellectual contributions. E.L.L. provided overall study supervision.

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