Online Supplementary Material

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eTable 1: Characteristics of studies included in the systematic review

Source Study Name	Population (Country)	Sample Size Study Design Age Range % Male	Impairment Definition	Baseline Impairment Prevalence (%)	Frailty Definition	Baseline Prevalence of Pre-Frailty & Frailty (%)	Statistical Methods	Confounders Adjusted For	Main Findings	NOS Score
Buttery et al., 2015 German Health Interview and Examination Survey for Adults (DEGS)	Western (Germany)	N=1843 Cross-Sectional 65-79 49.9	VI: Self-reported HI: Self-reported	VI: 4.8 HI: 6.3	Modified Fried frailty criteria	38.8 2.6	Multinomial logistic regression	age, sex, SES	VI was independently associated with: - frailty (vs. robustness): adjusted OR 3.81 (1.09-13.34); - pre-frailty: adjusted OR 2.24 (1.20-4.14). HI was independently associated with frailty (vs. robustness): adjusted OR 5.38 (2.17-13.35). However, HI was not independently associated with pre-frailty: adjusted OR 1.14 (0.71-1.84).	6/10
Çakmur, 2015 N.A.	Asian (Turkey)	N=168 Cross-Sectional ≥65 46.4	VI: Self-reported HI: Whisper test	VI: 7.7 HI: 10.1	Fried frailty criteria	47.3 7.1	Chi-square test	none	No significant difference in VI prevalence across frailty categories (p=0.134). Significantly higher prevalence of HI in frail elderly (p=0.036).	5/10
Chen et al., 2010 Taiwanese Survey of Health and Living Status of the Elderly	Asian (Taiwan)	N=2238 Cross-Sectional ≥65 51.2	VI: Self-reported HI: Self-reported	VI: 16.2 HI: 14.2	Modified Fried frailty criteria	40 4.8	Chi-square test	none	Significantly higher prevalence of VI in frail elderly (p<0.001). Significantly higher prevalence of HI in frail elderly (p<0.001).	6/10

Source **Study Name**	**Population (Country)**	**Sample Size** **Study Design** **Age Range** **% Male**	**Impairment Definition**	**Baseline Impairment Prevalence (%)**	**Frailty Definition**	**Baseline Prevalence of Pre-Frailty & Frailty (%)**	**Statistical Methods**	**Confounders Adjusted For**	**Main Findings**	**NOS Score**
Closs et al., 2016 The Multidimensional Study of the Elderly in the Family Health Strategy (EMI-SUS)	Western (Brazil)	N=521 Cross-Sectional ≥60 35.7	VI: Jaeger chart (worse than 20/40) for near VI HI: Whisper test	VI: 72.2 HI: 24	Fried frailty criteria	51.1 21.5	Chi-square test	none	Significantly higher prevalence of VI in frail elderly ($p<0.2$). Significantly higher prevalence of HI in frail elderly ($p<0.2$).	7/10
Doba et al., 2012 Japanese Health Research Volunteer Study	Asian (Japan)	N=407 Longitudinal >70 45.2	HI: (1) Self-reported; (2) Pure-tone audiometric hearing thresholds at 2000 and 4000 Hz in both ears	HI: 30	CSHA Clinical Frailty Scale	0 18.7	Multiple logistic regression	age, sex, height, weight, upper arm muscle area, calf circumference, bone mineral density, hand-grip of dominant side, slow timed walk, systolic pressure, pulse pressure, hemoglobin, luteinizing hormone, dehydroepiandrosterone sulfate, cognitive changes, history of a fall, living with a spouse, and urinary incontinence	HI was independently associated with increased incident frailty risk at 5-year follow-up from baseline robustness: OR 2.186 (1.197–3.995). Pure-tone audiometry results, analysed as continuous variables using the Student's t-test, were not significantly different between robust and frail groups (p=0.169, 0..580, 0.727, 0.976).	7/9
Eyigor et al., 2015 N.A.	Asian (Turkey)	N=1126 Cross-Sectional ≥65 34.3	VI: Self-reported HI: Self-reported	VI: 51.7 HI: 36	Fried frailty criteria	43.3 39.2	Multinomial logistic regression	age, sex, education, occupation, place of residence, physical activity, polypharmacy, comorbidity, incontinence, hospitalisation, emergency admission, avoidance of going outdoors, falls, insomnia, walking aid, musculoskeletal pain, fatigue, self-neglect, ambulation, malnutrition	VI was not independently associated with frailty (adjusted OR not reported and author uncontactable). HI was independently associated with frailty (vs. robustness): adjusted OR 1.983 (1.211-3.247).	7/10

Source Study Name	Population (Country)	Sample Size Study Design Age Range % Male	Impairment Definition	Baseline Impairment Prevalence (%)	Frailty Definition	Baseline Prevalence of Pre-Frailty & Frailty (%)	Statistical Methods	Confounders Adjusted For	Main Findings	NOS Score
Gu et al., 2019 National Basic Public Health Service Program (Fengxian district of Shanghai, China)	Asian (China)	N=4026 Cross-Sectional ≥60 41.5	HI: Self-reported	HI: 2.9	Fried frailty criteria	49.4 6.8	Multiple logistic regression	age, sex, hypertension, diabetes, COPD, stroke, CKD, physical activity, obesity, blindness, disability, anemia, total cholesterol, triglycerides	In univariate regression, HI was associated with prevalence of: - pre-frailty: OR 2.40, p<0.001, 95% CI unreported - frailty: OR 5.07, p<0.001, 95% CI unreported However, this attenuated on multivariate regression: - pre-frailty: adjusted OR 1.63, p=0.067, 95% CI unreported - frailty: adjusted OR 1.30, p=0.517, 95% CI unreported	8/10
Harita et al., 2019 Uchinada Olfactory and Gustatory Longevity Study	Asian (Japan)	N=141 Cross-Sectional 65-87 48.9	SI: objective Open Essence olfactory test score ≤7 TI: objective 1 mL whole mouth gustatory test for salty and sweet tastes	SI: 67.4 TI: 40.4 (salty); 9.2 (sweet)	Study of Osteoporotic Fractures (SOF) Frailty Criteria	35.4 12.8	Multiple logistic regression	age, sex, heart disease, digestive disease, bone/joint disease, BMI, body fat mass index, body mineral index and body protein index	SI was independently associated with any frailty after adjustment for all confounders except body protein index: OR 2.25 (1.01–5.03). However, after further adjustment for body protein index, the association lost its statistical significance: OR 2.07 (0.92–4.66).	7/10
Herr et al., 2018 Five Country Oldest Old Project (5-COOP)	Asian & Western (Japan, France, Switzerland, Sweden, Denmark)	N=741 Cross-Sectional ≥100 19.9	VI: Self-reported HI: Self-reported	VI: 44.8 HI: 35.3	Fried frailty criteria	29.4 64.7	Multiple Poisson regression	Country, interview mode, proxy interview, gender, institutionalised, musculoskeletal disease, diabetes, dementia, depression, disability ≥2 ADLs, falls in the past 6 months	VI was independently associated with a larger number of frailty criteria (count outcome): adjusted IRR 1.06 (1.01-1.11). HI was independently associated with a larger number of frailty criteria (count outcome): adjusted IRR 1.07 (1.02-1.12).	7/10

Source Study Name	Population (Country)	Sample Size Study Design Age Range % Male	Impairment Definition	Baseline Impairment Prevalence (%)	Frailty Definition	Baseline Prevalence of Pre-Frailty & Frailty (%)	Statistical Methods	Confounders Adjusted For	Main Findings	NOS Score
Kamil et al., 2016 Health, Aging and Body Composition (Health ABC) study	Western (USA)	N=2000 Longitudinal 70-79 47.1	HI: Pure-tone audiometric average of hearing thresholds at 0.5, 1, 2, and 4 kHz in the better hearing ear, where normal hearing ≤ 25 dB, mild HI = 26-40 dB, moderate-or-greater HI > 40 dB	HI: 58.4	Health ABC frailty criteria	0 1.8	Cox proportional hazards model	age, demographic characteristics (race, sex, education, and study site), and cardiovascular risk factors (hypertension, diabetes, stroke, and smoking history)	Moderate-or-greater HI was independently associated with increased risk of incident frailty at 10-year follow-up from baseline robustness: adjusted HR 1.63 (1.26-2.12). Mild HI was not associated with increased risk of incident frailty from baseline robustness: adjusted HR 1.12 (0.90-1.39). HI per 10 dB loss (continuous variable) was associated with increased risk of incident frailty at 10-year follow-up from baseline robustness: adjusted HR = 1.11 (1.03-1.19). No significant difference in HI prevalence across frailty categories at baseline (p=0.40).	6/9
Kamil et al., 2014 National Health and Nutrition Examination Survey (NHANES)	Western (USA)	N=2109 Cross-Sectional ≥70 Unreported	HI: Self-reported	HI: Unreported	Modified Fried frailty criteria	0 0	Multiple logistic regression	sex, race, education, income, BMI, smoking, hypertension, stroke, diabetes mellitus, general health status and hearing aid use	HI was independently associated with frailty: adjusted OR 1.68 (1.00–2.82). HI was independently associated with frailty in women (OR 3.79 [1.69-8.51]) but not men (OR 0.85 [0.44-1.66]).	8/10
Laudisio et al., 2019 InCHIANTI Study	Western (Italy)	N=1035 Cross-Sectional ≥65 44.3	SI: self-reported inability to recognise 2 or more of the smells – mint, coffee or air	SI: 57.0	Fried frailty criteria	40.6 10.7	Multiple logistic regression	age, sex, education, malignancy, peripheral arterial disease, angiotensin-converting enzyme inhibitor usage, benzodiazepine usage, glomerular filtration rate, depression (CES-D)	SI was independently associated with both: - frailty: OR 2.60 (1.39-4.85) - pre-frailty: OR 1.59 (1 17-2.16)	9/10

Source Study Name	Population (Country)	Sample Size Study Design Age Range % Male	Impairment Definition	Baseline Impairment Prevalence (%)	Frailty Definition	Baseline Prevalence of Pre-Frailty & Frailty (%)	Statistical Methods	Confounders Adjusted For	Main Findings	NOS Score
Liljas et al., 2017 English Longitudinal Study of Ageing (ELSA)	Western (England)	N=2836 Longitudinal ≥60 55.9	VI: Self-reported HI: Self-reported	VI: 12 HI: 22.7	Fried frailty criteria	41.5 9.2	Multiple logistic regression	age, sex, wealth, education, cardiovascular disease, diabetes, falls, cognition and depression	VI was independently associated with increased prevalence of: - pre-frailty: OR 1.56 (1.16-2.10) - frailty: OR 2.88 (1.83-4.54) - any frailty: OR 1.72 (1.30-2.29) VI was independently associated with incident any frailty at 4-year follow-up from baseline robustness: OR 2.07 (1.32-3.24) age and sex-adjusted; OR 1.86 (1.17-2.95) multi-adjusted. VI was not independently associated with incident frailty at 4-year follow-up from baseline pre-frailty: OR 1.34 (0.82-2.19) age and sex-adjusted. HI was independently associated with increased risk of incident any frailty at 4-year follow-up from baseline robustness: OR 1.43 (1.05–1.95) age and sex-adjusted. However, this was attenuated after multi-adjustment: OR 1.32 (0.96–1.81). HI was independently associated with increased risk of incident frailty from baseline pre-frailty: OR 1.57 (1.01-2.44), multi-adjusted.	8/9
Lorenzo-López et al., 2019 VERISAÚDE study	Western (Spain)	N=736 Longitudinal ≥65 39.4	VI: Snellen (corrected vision worse than 20/50) HI: Whisper test	VI: 8.6 HI: 27	Fried frailty criteria	71.8 3.7	VI: Chi-square test HI: Multiple logistic regression	VI: none HI: age, hearing impairment, congestive heart failure, number of medications and polypharmacy	Among participants with VI, there was no significant difference between the number of participants whose frailty worsened or improved at 1 year follow-up (p-value not reported). HI was independently associated with increased risk of worsening frailty at 1-year follow-up: OR 3.180 (1.078-9.384).	VI: 5/9 HI: 7/9

Source Study Name	Population (Country)	Sample Size Study Design Age Range % Male	Impairment Definition	Baseline Impairment Prevalence (%)	Frailty Definition	Baseline Prevalence of Pre-Frailty & Frailty (%)	Statistical Methods	Confounders Adjusted For	Main Findings	NOS Score
Mohd Hamidin et al., 2018 N.A.	Asian (Malaysia)	N=279 Cross-Sectional ≥60 42.3	VI: Self-reported HI: Self-reported	VI: 62.4 HI: 19	Modified Fried frailty criteria	41.6 18.3	VI: Chi-square test HI: Multiple logistic regression	VI: none HI: age, marital status, education, appetite loss, hospitalisation in past year, self-rated health, BMI, lean body mass	No significant difference in VI prevalence across frailty categories (p=0.133). HI had a positive but not statistically significant association with frailty (reference: robustness + pre-frailty): OR 2.20 (0.91–5.37).	VI: 7/10 HI: 9/10
Naharci et al., 2019 Healthy Aging Research Initiative (HARI)	Western (USA)	N=484 Cross-Sectional ≥60 28.1	HI: Self-reported	HI: 25.6	Modified Fried frailty criteria	unreported 16.3	Multiple logistic regression	age, gender, body mass index, smoking history, regular alcohol drinker, hypertension, and diabetes mellitus	HI was independently associated with increased prevalence of frailty: OR 3.064 (1.42-6.60).	7/10
Ng et al., 2014 Singapore Longitudinal Ageing Studies (SLAS)	Asian (Singapore)	N=1685 Cross-Sectional ≥55 35.7	VI: Snellen (corrected binocular vision worse than 20/40) HI: Whisper test	VI: 26.7 HI: 2.8	Modified Fried frailty criteria	42.3 5.3	Multiple logistic regression	age, sex, education, size of public housing, ethnicity, marital status, living alone, current smoker, daily alcohol intake, number of chronic medical conditions (>5), cardiovascular disease, hypertension, diabetes, stroke, coronary heart disease, atrial fibrillation, heart failure, cataracts/glaucoma, asthma/COPD, thyroid disease, arthritis, osteoporosis, gastrointestinal problems, cancer, chronic kidney disease, self-rated health, depression (GDS15), cognitive impairment (MMSE score 23), polypharmacy (>5 drugs), postural hypotension, obesity (BMI ≥30), nutritional risk score, albumin, anemia, total cholesterol, lymphocyte counts, white cell count	VI was independently associated with any frailty: adjusted OR 1.52 (1.19–1.95). HI was independently associated with any frailty: adjusted OR 2.34 (1.21-4.52).	9/10

Source Study Name	Population (Country)	Sample Size Study Design Age Range % Male	Impairment Definition	Baseline Impairment Prevalence (%)	Frailty Definition	Baseline Prevalence of Pre-Frailty & Frailty (%)	Statistical Methods	Confounders Adjusted For	Main Findings	NOS Score
Samper-Ternent et al., 2008 Hispanic Established Population for the Epidemiological Study of the Elderly (H-EPESE)	Western (USA)	N=1370 Cross-Sectional ≥65 41	VI: Modified directional "E" Snellen (worse than 20/40)	VI: 4.9	Fried frailty criteria	45.7 4.4	Chi-square test	none	No significant difference in VI prevalence across frailty categories (p≥0.05).	7/10
Somekawa et al., 2017 N.A.	Asian (Japan)	N=768 Cross-Sectional ≥65 43.1	SI: Self-reported Appetite, Hunger, Sensory Perception (AHSP) questionnaire, where SI = smell score <18.5/30 TI: Self-reported AHSP, where TI = taste score <26.5/40	SI: 48.0 TI: 61.7	Modified Fried frailty criteria	? 5.9	Multiple logistic regression	age, sex, IADL and chronic conditions (presence of any one: hypertension, stroke, heart disease, diabetes, hyperlipidemia, osteoporosis, anemia, chronic renal failure, bronchial asthma and chronic obstructive pulmonary disease)	SI was not independently associated with frailty: OR 1.73 (0.83-3.63). TI was independently associated with frailty: OR 2.81 (1.29-6.12).	7/10

Source Study Name	Population (Country)	Sample Size Study Design Age Range % Male	Impairment Definition	Baseline Impairment Prevalence (%)	Frailty Definition	Baseline Prevalence of Pre-Frailty & Frailty (%)	Statistical Methods	Confounders Adjusted For	Main Findings	NOS Score
Swenor et al., 2020 Women's Health and Ageing Study (WHAS) III	Western (USA)	N=796 Longitudinal mean 75 55.6	VI: Snellen (presenting binocular vision worse than 20/40)	VI: 63	Modified Fried frailty criteria	47.7 13.7	Ordinal logistic regression	age (cubic spline), race, smoking status, diabetic status, total number of comorbidities	VI was independently associated with frailty prevalence at baseline: adjusted OR 5.12 (3.90-6.74). Among baseline robust participants, individuals with mild VI were more likely to progress toward incident frailty at 3-year follow-up: OR 2.2 (0.9-5.4), though this was not statistically significant. However, individuals with moderate/severe VI had significantly greater odds of progressing toward incident frailty: OR 3.5 (1.4-8.4).	8/9
Swenor et al., 2020 National Health and Nutrition Examination Survey (NHANES) 1999-2002	Western (USA)	N=2639 Cross-Sectional ≥60 44.4	VI: Snellen (presenting better-eye vision worse than 20/40)	VI: 9	Modified Fried frailty criteria	33.6 8	Multinomial logistic regression	age (cubic spline), sex, race, smoking status, diabetic status, total number of comorbidities	VI was independently associated with increased prevalence of: - pre-frailty: adjusted OR 3.15 (1.89-5.26); - frailty: adjusted OR 3.66 (1.46–9.19).	9/10
Trevisan et al., 2017 Progetto Veneto Anziani Longitudinal Study (Pro.V.A.)	Western (Italy)	N=2925 Longitudinal ≥65 40.3	VI: Self-reported HI: Self-reported	VI: 43.3 HI: 76	Modified Fried frailty criteria	49.3 7.6	Multiple logistic regression	VI: age, sex, BMI, marital status, educational level, monthly income, smoking, drinking habits, living situation, diabetes mellitus, anemia, CVD, cancer, osteoarthritis, serum 25(OH)D, serum uric acid, ADL score, IADL score, daily medications HI: age, sex	At 4.4-year follow-up, VI was independently associated with increased risk of: - incident any frailty: adjusted OR 1.37 (1.24-1.49), p<0.001; - incident frailty (vs. pre-frailty): adjusted OR 1.18 (1.05-1.33), p<0.01. HI was independently associated with increased risk of incident any frailty at 4.4-year follow-up from baseline robustness: adjusted OR 1.13 (1.03-1.23) but not incident frailty from baseline pre-frailty: adjusted OR 1.05 (0.93-1.20).	VI: 8/9 HI: 7/9

Source Study Name	Population (Country)	Sample Size Study Design Age Range % Male	Impairment Definition	Baseline Impairment Prevalence (%)	Frailty Definition	Baseline Prevalence of Pre-Frailty & Frailty (%)	Statistical Methods	Confounders Adjusted For	Main Findings	NOS Score
Varadaraj et al., 2020 National Health and Nutrition Examination Survey (NHANES) 1999-2002	Western (USA)	N=2705 Cross-Sectional ≥60 44	VI: Unspecified near chart (presenting binocular vision worse than 20/40) and self-reported near VI	VI: 13	Modified Fried frailty criteria	32.6 7.5	Multinomial logistic regression	age (cubic spline), sex, race, education, smoking, diabetes, and total number of comorbidities	Presenting near VI was independently associated with increased prevalence of: - pre-frailty: OR 1.6 (1.1-2.3); - frailty: OR 2.5 (1.4-4.3) Self-reported near VI was independently associated with increased prevalence of: - pre-frailty: OR 2.9 (1.8-4.7) - frailty: OR 4.3 (2.2-8.3)	8/10
Yang et al., 2019 N.A.	Asian (China)	N=507 Longitudinal ≥65 40.2	VI: Self-reported	VI: 64.7	FRAIL scale	26.2 11.2	Multiple logistic regression	age, marital status, cognitive impairment, disability, BMI	VI was independently associated with worsening frailty at 3-year follow-up: adjusted OR 2.02 (1.27-3.22).	6/9

Abbreviations: VI, vision impairment; HI, hearing impairment; TI, taste impairment; SI, smell impairment; OR, odds ratio; HR, hazard ratio; dB, decibel; SES; socioeconomic status; BMI, body mass index; ADL, activities of daily living; IADL, instrumental activities of daily living; CES-D, Center for Epidemiological Studies-Depression (CES-D); GDS15, Geriatric Depression Scale-15; MMSE, Mini-Mental State Examination; AHSP, Appetite, Hunger, Sensory Perception.
Lorenzo-Lopez et al. (2019) reported only longitudinal associations between VI/HI and frailty transitions. For the purposes of this cross-sectional meta-analysis, they kindly provided baseline cross-sectional associations for both VI and HI.
Swenor et al. (2020), in the WHAS III study, categorised VI as: no VI, mild VI and moderate-or-greater VI. For the purposes of this meta-analysis, where most studies used a binary definition of VI, they kindly provided the relevant adjusted ORs via personal communication.
Trevisan et al. (2017) kindly provided, via personal communication, the age and sex-adjusted ORs for the associations of HI with incident any frailty from baseline robustness and incident frailty from baseline pre-frailty.
Yang et al. (2019) included mortality in their definition of "worsening frailty".

eTable 2: Meta-analyses in subgroups, stratified by categorical study-level characteristics

	Odds of pre-frailty				Odds of frailty				Odds of frailty (vs. pre-frailty)				Odds of any frailty			
	Studies	**OR (95% CI)**	**P**	**I^2**	**Studies**	**OR (95% CI)**	**P**	**I^2**	**Studies**	**OR (95% CI)**	**P**	**I^2**	**Studies**	**OR (95% CI)**	**P**	**I^2**
VISION IMPAIRMENT																
Overall	12	1.84 (1.53, 2.20)	<0.001	58.9	12	3.16 (2.27, 4.40)	<0.001	66.3	12	1.91 (1.56, 2.35)	<0.001	55.7	12	2.26 (1.84, 2.79)	<0.001	76.4
Covariate-adjusted																
No	8	1.68 (1.35, 2.10)	<0.001	61.9	7	3.27 (2.34, 4.55)	<0.001	51.3	11	1.86 (1.51, 2.27)	<0.001	55.6	10	2.32 (1.84, 2.91)	<0.001	74.5
Yes	4	2.21 (1.59, 3.07)	<0.001	55.8	5	3.21 (1.49, 6.91)	0.003	79.2	1	–	–	–	2	2.08 (1.08, 4.00)	0.027	87.3
Race																
Asian	4	1.93 (1.49, 2.51)	<0.001	66.3	4	2.60 (1.23, 5.48)	0.012	86.9	4	1.58 (1.10, 2.27)	0.013	66.1	4	1.93 (1.40, 2.67)	<0.001	79.1
Caucasian	8	1.78 (1.37, 2.31)	<0.001	56.9	8	3.22 (2.46, 4.22)	<0.001	9.9	8	2.19 (1.87, 2.56)	<0.001	0.0	8	2.49 (1.91, 3.24)	<0.001	71.2
Risk of bias																
NOS < 8	8	1.70 (1.33, 2.18)	<0.001	58.5	8	2.79 (1.80, 4.32)	<0.001	68.0	8	1.78 (1.35, 2.34)	<0.001	57.2	8	2.10 (1.61, 2.73)	<0.001	68.5
NOS ≥ 8	4	2.05 (1.54, 2.73)	<0.001	64.7	4	3.87 (2.40, 6.23)	<0.001	55.9	4	2.14 (1.63, 2.82)	<0.001	38.3	4	2.55 (1.78, 3.66)	<0.001	85.4
Frailty definition																
Fried criteria	6	**1.52 (1.28, 1.80)**	**<0.001**	0.0	6	2.40 (1.66, 3.49)	<0.001	48.0	6	1.93 (1.39, 2.68)	<0.001	72.8	6	1.98 (1.54, 2.55)	<0.001	54.2
Modified Fried	6	**2.21 (1.77, 2.77)**	**<0.001**	53.8	6	4.19 (2.68, 6.55)	<0.001	59.8	6	1.90 (1.55, 2.34)	<0.001	0.0	6	2.56 (1.85, 3.54)	<0.001	84.4
Measure of impairment																
Objective	6	1.91 (1.46, 2.51)	<0.001	57.3	6	3.71 (2.57, 5.34)	<0.001	28.4	6	1.93 (1.54, 2.41)	<0.001	0.0	6	2.08 (1.50, 2.90)	<0.001	78.3
Self-reported	6	1.76 (1.35, 2.30)	<0.001	65.3	6	2.65 (1.59, 4.42)	<0.001	77.3	6	1.82 (1.32, 2.51)	<0.001	75.0	6	2.45 (1.87, 3.20)	<0.001	72.4

	Odds of pre-frailty				Odds of frailty				Odds of frailty (vs. pre-frailty)				Odds of any frailty			
	Studies	**OR (95% CI)**	**P**	**I^2**	**Studies**	**OR (95% CI)**	**P**	**I^2**	**Studies**	**OR (95% CI)**	**P**	**I^2**	**Studies**	**OR (95% CI)**	**P**	**I^2**
HEARING IMPAIRMENT																
Overall	10	1.61 (1.28, 2.01)	<0.001	65.2	10	2.53 (1.88, 3.41)	<0.001	53.4	10	1.87 (1.47, 2.39)	<0.001	61.3	11	1.92 (1.49, 2.47)	<0.001	76.4
Covariate-adjusted																
No	8	1.68 (1.29, 2.19)	<0.001	71.2	7	2.66 (1.88, 3.75)	<0.001	52.2	10	1.87 (1.47, 2.39)	<0.001	61.3	8	2.03 (1.45, 2.85)	<0.001	80.4
Yes	2	1.34 (0.94, 1.91)	0.101	0.0	3	2.30 (1.10, 4.81)	0.027	68.2					3	1.55 (1.22, 1.96)	<0.001	16.0
Race																
Asian	4	**2.18 (1.80, 2.65)**	**<0.001**	0.0	4	2.36 (1.73, 3.22)	<0.001	0.0	4	1.47 (1.13, 1.92)	0.004	14.1	4	2.36 (1.95, 2.84)	<0.001	0.0
Caucasian	6	**1.32 (1.07, 1.62)**	**0.011**	34.8	6	2.66 (1.55, 4.56)	<0.001	76.3	6	2.19 (1.63, 2.93)	<0.001	59.6	7	1.75 (1.21, 2.53)	0.003	82.6
Risk of bias																
NOS < 8	6	1.58 (1.12, 2.23)	0.010	74.6	6	2.88 (1.82, 4.57)	<0.001	66.5	6	1.99 (1.37, 2.88)	<0.001	76.2	6	1.94 (1.25, 3.01)	0.003	86.5
NOS ≥ 8	4	1.55 (1.24, 1.94)	<0.001	16.0	4	2.11 (1.64, 2.72)	<0.001	0.0	4	1.66 (1.30, 2.13)	<0.001	4.5	5	1.90 (1.41, 2.55)	<0.001	52.7
Frailty definition																
Fried criteria	6	1.49 (1.13, 1.96)	0.005	62.6	6	2.29 (1.47, 3.57)	<0.001	71.5	6	1.91 (1.52, 2.40)	<0.001	53.2	6	2.00 (1.27, 3.16)	0.003	87.7
Modified Fried	4	1.82 (1.26, 2.63)	0.001	56.1	4	2.97 (2.06, 4.29)	<0.001	0.0	4	1.80 (0.86, 3.80)	0.121	74.8	5	1.90 (1.49, 2.44)	<0.001	36.4
Measure of impairment																
Objective	3	1.38 (0.78, 2.43)	0.267	73.7	3	2.07 (1.09, 3.94)	0.027	42.1	3	1.62 (0.93, 2.80)	0.086	35.2	3	1.49 (0.85, 2.63)	0.168	74.3
Self-reported	7	1.72 (1.38, 2.16)	<0.001	54.2	7	2.73 (1.87, 3.99)	<0.001	65.6	7	1.96 (1.45, 2.64)	<0.001	73.0	8	2.09 (1.61, 2.71)	<0.001	72.4

Abbreviations: NOS, Newcastle-Ottawa Scale.

OR, 95% CI, P and I^2 for subgroups with only 1 constituent study are not reported and instead indicated with a dash (–).

Red ORs indicate significant effect modification based on a random-effects meta-regression analysis (eTable 3).

Highlighted numbers indicate the 95% CI (lower bound) and P-values for subgroups where the pooled OR was non-significant.

We urge readers to exercise caution in interpreting these exploratory analyses, especially for subgroups with few constituent studies.

eTable 3: Random-effects meta-regression of logORs against potential effect modifiers (continuous and categorical study-level characteristics)

	Odds of pre-frailty		Odds of frailty		Odds of frailty (vs. pre-frailty)		Odds of any frailty	
	Beta‡ (95% CI)	P	Beta‡ (95% CI)	P	Beta‡ (95% CI)	P	Beta‡ (95% CI)	P
VISION IMPAIRMENT								
Aged ≥ 75 years (per 5% increase)	0.98 (0.94, 1.02)	0.369	1.00 (0.93, 1.07)	0.890	1.01 (0.97, 1.06)	0.535	1.00 (0.95, 1.06)	0.970
Female % (per 5% increase)	0.93 (0.84, 1.02)	0.106	0.91 (0.79, 1.05)	0.182	0.98 (0.89, 1.08)	0.636	0.89 (0.81, 0.97)	**0.013**
Frailty prevalence (per 5% increase)	0.96 (0.91, 1.01)	0.079	0.93 (0.86, 1.01)	0.075	0.99 (0.94, 1.04)	0.651	0.97 (0.91, 1.03)	0.316
Analytical model								
Unadjusted	Reference		Reference		Reference		Reference	
Covariate-adjusted	1.31 (0.88, 1.95)	0.180	0.95 (0.47, 1.94)	0.890			0.89 (0.51, 1.56)	0.684
Race								
Asian	Reference		Reference		Reference		Reference	
Caucasian	0.93 (0.63, 1.36)	0.699	1.32 (0.65, 2.71)	0.442	1.40 (0.97, 2.03)	0.073	1.29 (0.85, 1.97)	0.236
Study design								
Cross-sectional study design	Reference		Reference		Reference		Reference	
Cohort study design								
Risk of bias								
NOS < 8	Reference		Reference		Reference		Reference	
NOS ≥ 8	1.21 (0.82, 1.79)	0.339	1.43 (0.70, 2.92)	0.323	1.22 (0.80, 1.87)	0.360	1.22 (0.79, 1.88)	0.379
Frailty definition								
Fried criteria	Reference		Reference		Reference		Reference	
Modified Fried or other criteria	1.47 (1.11, 1.96)	**0.008**	1.74 (0.97, 3.11)	0.063	1.01 (0.66, 1.55)	0.974	1.30 (0.86, 1.97)	0.207
Impairment definition								
Objectively rated	Reference		Reference		Reference		Reference	
Self-reported	0.92 (0.63, 1.35)	0.682	0.68 (0.35, 1.35)	0.273	0.89 (0.58, 1.38)	0.601	1.17 (0.76, 1.79)	0.477

	Odds of pre-frailty		Odds of frailty		Odds of frailty (vs. pre-frailty)		Odds of any frailty	
	Beta‡ (95% CI)	**P**	**Beta‡ (95% CI)**	**P**	**Beta‡ (95% CI)**	**P**	**Beta‡ (95% CI)**	**P**
HEARING IMPAIRMENT								
Aged ≥ 75 years (per 5% increase)	1.01 (0.95, 1.08)	0.748	1.05 (0.99, 1.12)	0.105	1.02 (0.97, 1.08)	0.352	1.04 (0.97, 1.12)	0.228
Female % (per 5% increase)	1.05 (0.93, 1.19)	0.420	1.08 (0.93, 1.25)	0.311	1.06 (0.96, 1.16)	0.245	1.13 (0.99, 1.30)	0.075
Frailty prevalence (per 5% increase)	1.05 (0.98, 1.12)	0.171	1.07 (0.99, 1.15)	0.084	1.03 (0.97, 1.09)	0.317	1.09 (1.02, 1.17)	**0.014**
Analytical model								
Unadjusted	Reference		Reference		Reference		Reference	
Covariate-adjusted	0.81 (0.45, 1.46)	0.477	0.84 (0.42, 1.70)	0.637			0.84 (0.47, 1.51)	0.558
Race								
Asian	Reference		Reference		Reference		Reference	
Caucasian	0.61 (0.47, 0.79)	**<0.001**	1.09 (0.55, 2.13)	0.811	1.52 (0.96, 2.39)	0.071	0.72 (0.44, 1.17)	0.181
Study design								
Cross-sectional study design	Reference		Reference		Reference		Reference	
Cohort study design								
Risk of bias								
NOS < 8	Reference		Reference		Reference		Reference	
NOS ≥ 8	1.06 (0.65, 1.73)	0.820	0.74 (0.39, 1.39)	0.350	0.86 (0.50, 1.47)	0.573	1.02 (0.60, 1.75)	0.940
Frailty definition								
Fried criteria	Reference		Reference		Reference		Reference	
Modified Fried or other criteria	1.23 (0.78, 1.93)	0.378	1.36 (0.71, 2.60)	0.354	0.94 (0.53, 1.66)	0.838	0.97 (0.57, 1.67)	0.922
Impairment definition								
Objectively rated	Reference		Reference		Reference		Reference	
Self-reported	1.30 (0.81, 2.11)	0.279	1.32 (0.62, 2.82)	0.470	1.22 (0.64, 2.32)	0.544	1.44 (0.83, 2.50)	0.200

Abbreviations: NOS, Newcastle-Ottawa Scale.

Red P-values indicate significant effect modification by the given study-level characteristic for the relevant meta-analysis.

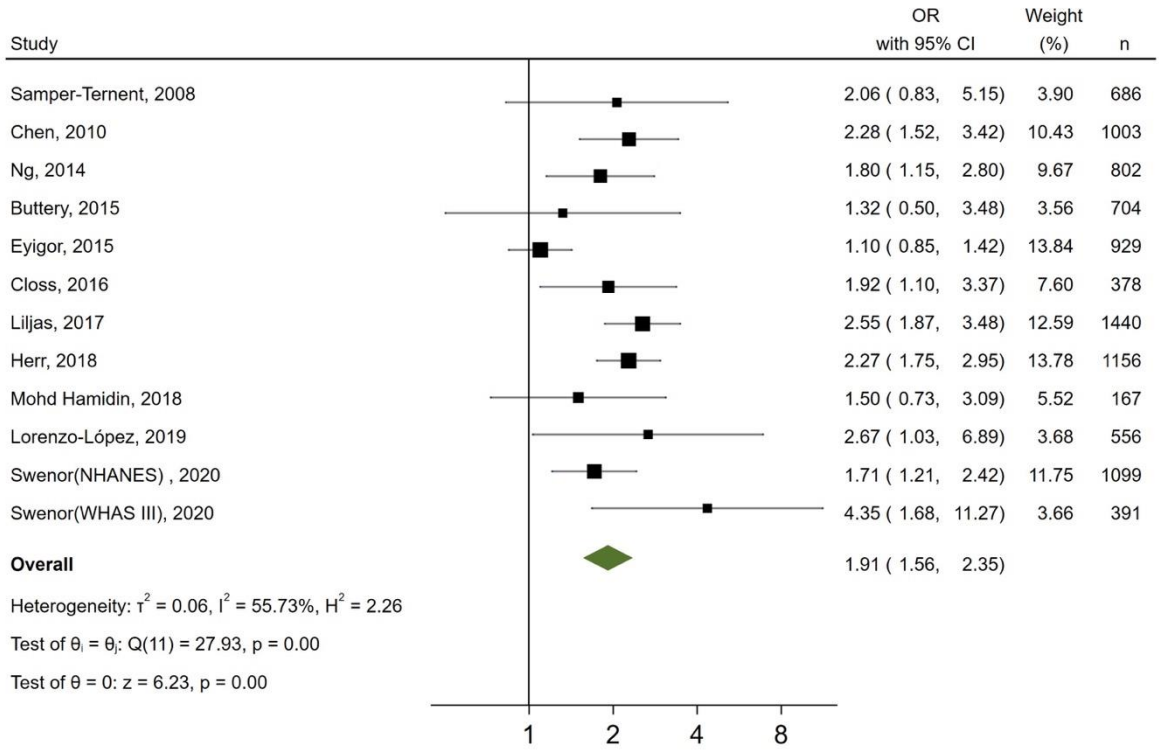
‡ Estimated factor by which the OR changes per unit increase in a continuous variable or in comparison with the reference group for a categorical variable

eTable 4: Meta-analyses with publication bias assessment

		Participant number			Meta-analysis			Publication bias
	Studies	Total	Group 1	Group 0	OR (95% CI)	P	I^2	Egger bias, P
VISION IMPAIRMENT								
Odds of prefrailty	12	14856	7820	7036	1.84 (1.53, 2.20)	<0.001	58.9	-0.65, 0.600
Odds of frailty	12	10095	7820	2275	3.16 (2.27, 4.40)	<0.001	66.3	0.93, 0.499
Odds of frailty (vs. prefrailty)	12	9311	7036	2275	1.91 (1.56, 2.35)	<0.001	55.7	0.64, 0.468
Odds of any frailty	12	17131	7820	9311	2.26 (1.84, 2.79)	<0.001	76.4	-1.15, 0.453
HEARING IMPAIRMENT								
Odds of prefrailty	10	14329	7125	7204	1.61 (1.28, 2.01)	<0.001	65.2	0.86, 0.510
Odds of frailty	10	9332	7125	2207	2.53 (1.88, 3.41)	<0.001	53.4	0.61, 0.636
Odds of frailty (vs. prefrailty)	10	9411	7204	2207	1.87 (1.47, 2.39)	<0.001	61.3	-0.30, 0.783
Odds of any frailty	11	18645	7125*	9411*	1.92 (1.49, 2.47)	<0.001	76.4	2.48, 0.094

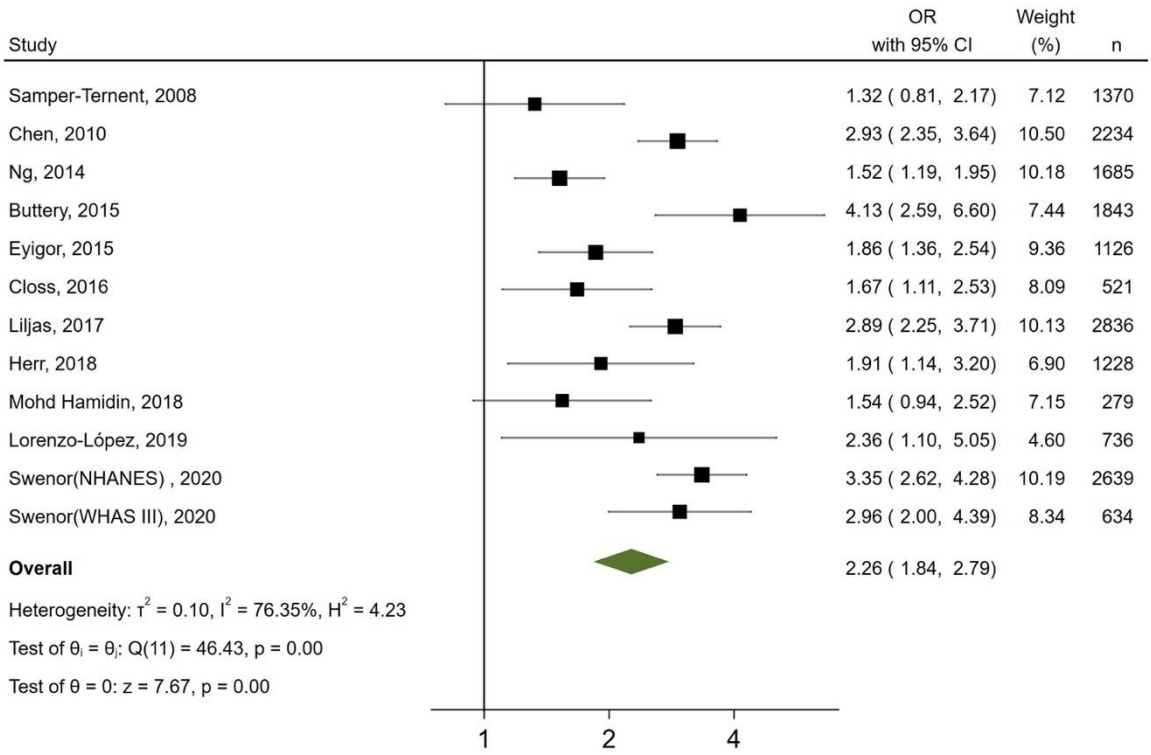
* Numbers excluded in total 2109 individuals from Kamil's study as the breakdown was not available.
Egger bias did not detect any funnel plot asymmetry.

eFigure 1: Random-effects meta-analyses of the cross-sectional association between vision impairment and frailty (vs. pre-frailty)



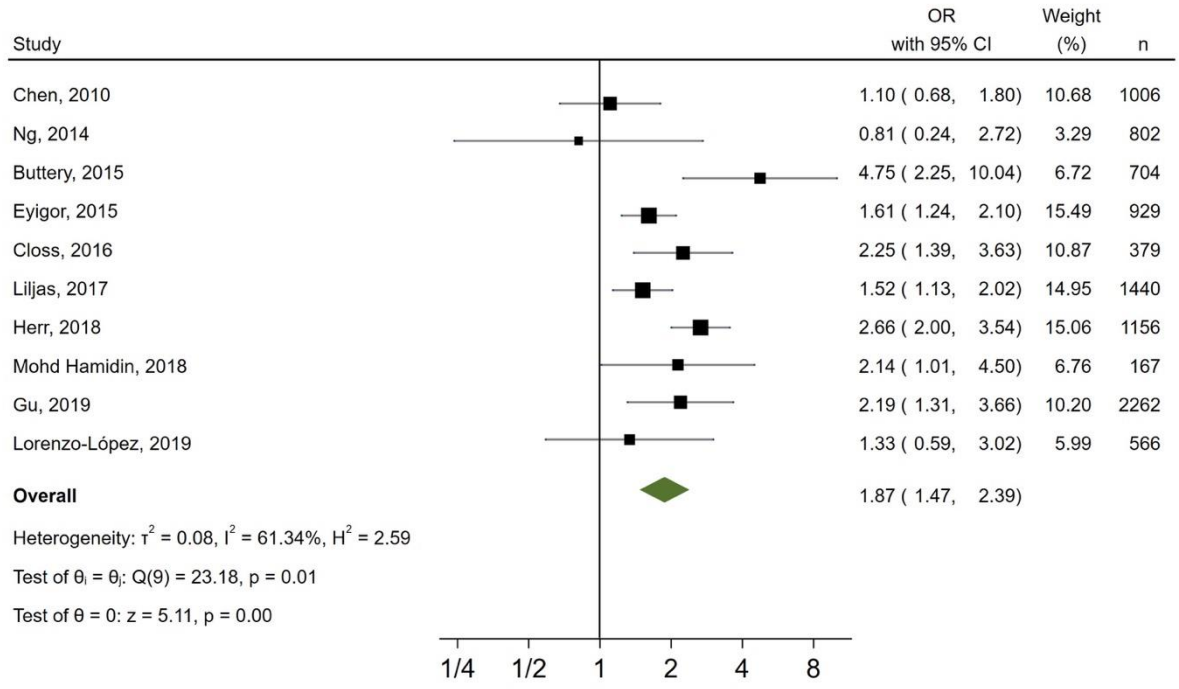
Green diamonds are the estimated pooled odds ratio (OR) for each meta-analysis; box sizes reflect the relative weight apportioned to studies in the meta-analysis. N=9,311.

eFigure 2: Random-effects meta-analyses of the cross-sectional association between vision impairment and any frailty (i.e. combined pre-frailty/frailty)



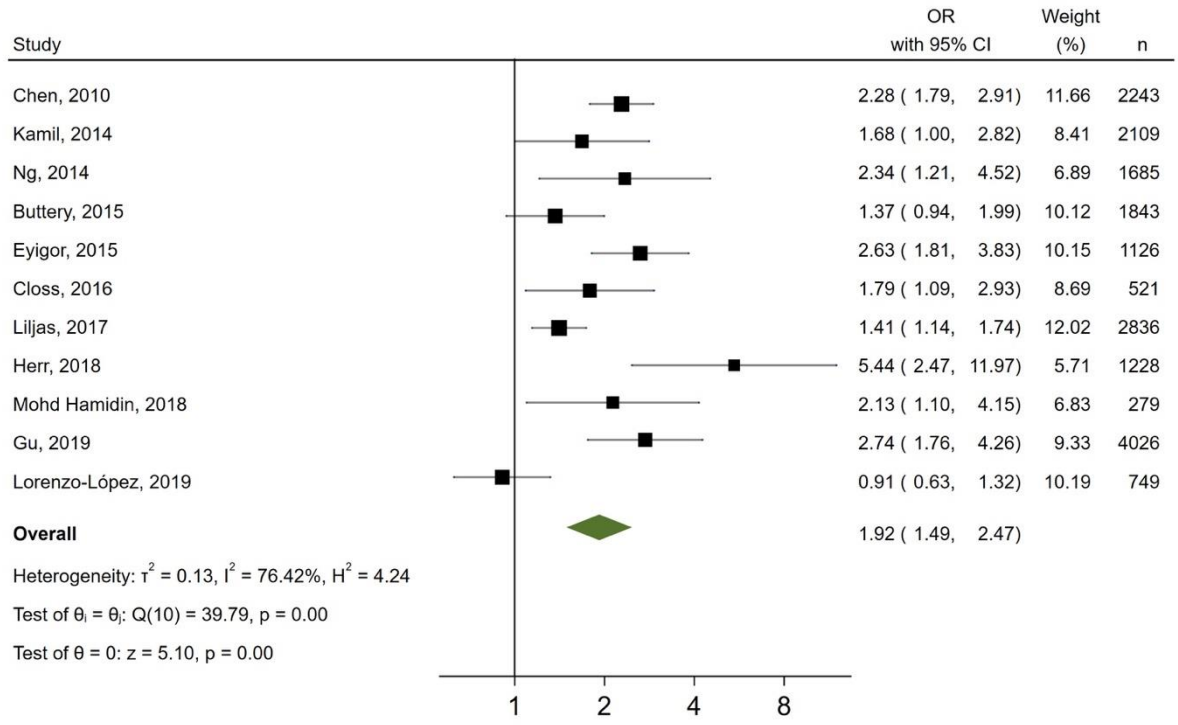
Green diamonds are the estimated pooled odds ratio (OR) for each meta-analysis; box sizes reflect the relative weight apportioned to studies in the meta-analysis. N=17,131.

eFigure 3: Random-effects meta-analyses of the cross-sectional association between hearing impairment and frailty (vs. pre-frailty)



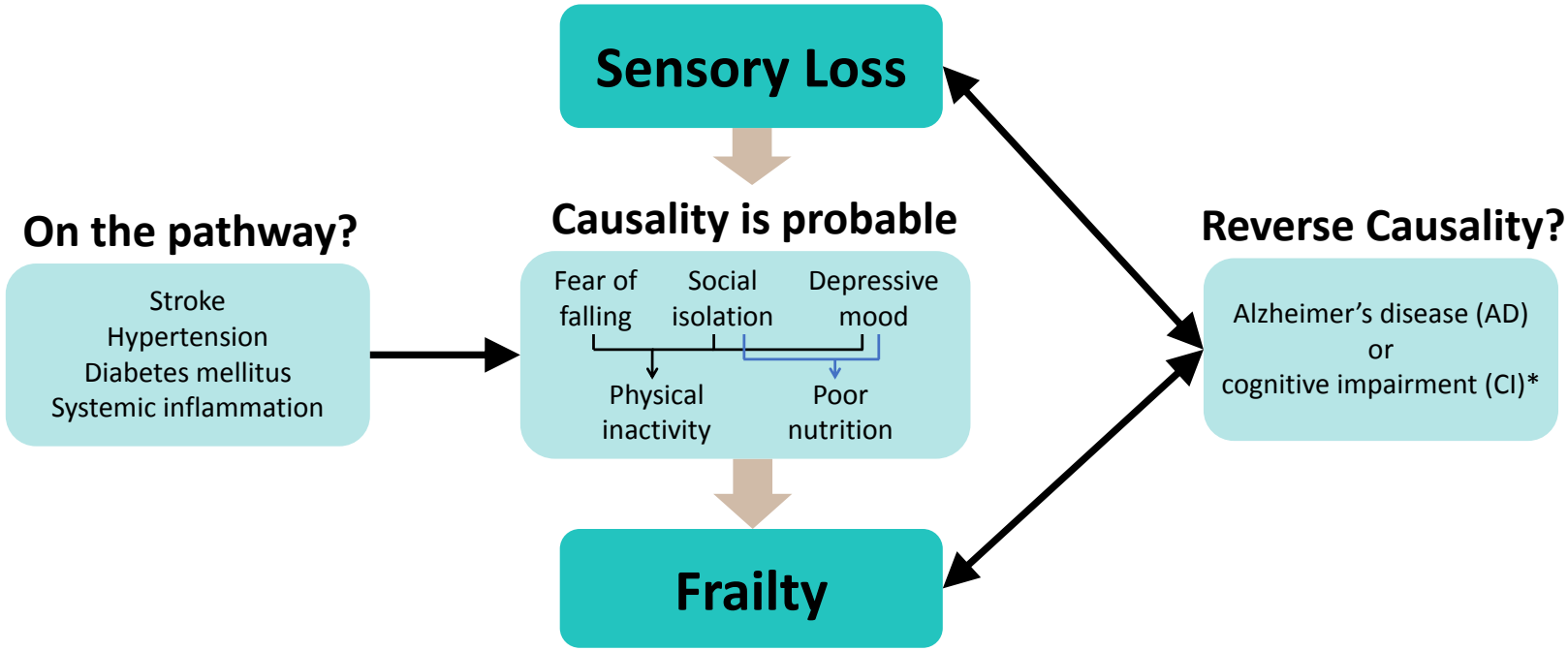
Green diamonds are the estimated pooled odds ratio (OR) for each meta-analysis; box sizes reflect the relative weight apportioned to studies in the meta-analysis. N=9,411.

eFigure 4: Random-effects meta-analyses of the cross-sectional association between hearing impairment and any frailty (i.e. combined pre-frailty/frailty)



Green diamonds are the estimated pooled odds ratio (OR) for each meta-analysis; box sizes reflect the relative weight apportioned to studies in the meta-analysis. N=18,645.

eFigure 5: Schematic depiction of discussion



Established epidemiologic associations suggest a causal relationship between sensory loss and frailty. Other possibilities include confounding and reverse causality. *AD and CI can act as a causal pathway, reverse causal pathway or confounder; this has been simplified here for brevity. Please refer to main text for precise relationships.

eMethods 1: Detailed Search Strategy

PubMed

Free Text
Initial search performed on 30 April 2019
Search updated on 5 May 2020
No limits applied

#	Search Term	No. of Results
1	"vision" OR "visual" OR "sight" OR "seeing" OR "eyesight"	639,483
2	"hearing" OR "auditory" OR "audition" OR "aural"	230,363
3	"smell" OR "olfactory" OR "olfaction"	60,355
4	"taste" OR "gustatory" OR "gustation"	44,042
5	"sensory" OR "sensorial" OR "sensation"	254,877
6	"loss" OR "impairment" OR "dysfunction" OR "decline" OR reduc* OR decreas* OR diminish* OR difficult* OR problem* OR "trouble" OR "issues" OR deficit* OR deficien* OR insufficien* OR "hard" OR "poor" OR "bad" OR "low"	10,061,322
7	(1 OR 2 OR 3 OR 4 OR 5) AND 6	546,651
8	"blindness" OR "deafness" OR "presbycusis" OR "anosmia" OR "hyposmia" OR "microsmia" OR "ageusia" OR "hypogeusia"	85,628
9	7 OR 8	596,474
10	"frailty"	14,353
11	9 AND 10	384

Controlled Vocabulary: Medical Subject Headings (MeSH)
Initial search performed on 30 April 2019
Search updated on 5 May 2020
No limits applied

#	Search Term	No. of Results
1	("Vision Disorders"[MeSH]) AND "Frailty"[MeSH]	2
2	("Hearing Loss"[MeSH]) AND "Frailty"[MeSH]	3
3	("Ageusia"[MeSH] OR "Taste Disorders"[MeSH] OR "Taste Threshold"[MeSH] OR "Taste Perception"[MeSH]) AND "Frailty"[MeSH]	1
4	("Olfaction Disorders"[MeSH]) AND "Frailty"[MeSH]	0
5	("Sensation Disorders"[MeSH]) AND "Frailty"[MeSH]	8

All MeSH search results had already been found in the free-text search.

Embase

Free Text
Initial search performed on 30 April 2019
Search updated on 5 May 2020
[embase]/lim, no other limits applied

Mapping options enabled:

- map to preferred term in Emtree
- search also as free text in all fields
- explode using narrower Emtree terms
- search as broadly as possible

#	Search Term	No. of Results
1	(("vision" OR "visual" OR "sight" OR "seeing" OR "eyesight" OR "hearing" OR "auditory" OR "audition" OR "aural" OR "smell" OR "olfactory" OR "olfaction" OR "taste" OR "gustatory" OR "gustation" OR "sensory" OR "sensorial" OR "sensation") AND ("loss" OR "impairment" OR "dysfunction" OR "decline" OR reduc* OR decreas* OR diminish* OR difficult* OR problem* OR "trouble" OR "issues" OR deficit* OR deficien* OR insufficien* OR "hard" OR "poor" OR	657

	"bad" OR "low") OR ("blindness" OR "deafness" OR "presbycusis" OR "anosmia" OR "hyposmia" OR "microsmia" OR "ageusia" OR "hypogeusia")) AND "frailty"	

Cochrane Database of Systematic Reviews

Free Text
Initial search performed on 30 April 2019
Search updated on 5 May 2020
Word variations excluded (the default function in advanced search, for greater precision)
No other limits applied

#	Search Term	No. of Results
1	"vision" OR "visual" OR "sight" OR "seeing" OR "eyesight"	5202
2	"hearing" OR "auditory" OR "audition" OR "aural"	850
3	"smell" OR "olfactory" OR "olfaction"	285
4	"taste" OR "gustatory" OR "gustation"	462
5	"sensory" OR "sensorial" OR "sensation"	1305
6	"loss" OR "impairment" OR "dysfunction" OR "decline" OR reduc* OR decreas* OR diminish* OR difficult* OR problem* OR "trouble" OR "issues" OR deficit* OR deficien* OR insufficien* OR "hard" OR "poor" OR "bad" OR "low"	9776
7	(1 OR 2 OR 3 OR 4 OR 5) AND 6	5849
8	"blindness" OR "deafness" OR "presbycusis" OR "anosmia" OR "hyposmia" OR "microsmia" OR "ageusia" OR "hypogeusia"	769
9	7 OR 8	5964
10	"frailty"	74
11	9 AND 10	49

Controlled Vocabulary: Medical Subject Headings (MeSH)
Initial search performed on 30 April 2019
Search updated on 5 May 2020
No limits applied

#	Search Term	No. of Results
1	Sensation Disorders [MeSH] explode all trees	5357
2	Frailty [MeSH] explode all trees	91
3	1 AND 2	0

eMethods 2: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eMethods 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-7, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5, 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (**including specification of whether this was done at the study or outcome level**), and how this information is to be used in any data synthesis.	7
Summary measures	13	**State the principal summary measures (e.g., risk ratio, difference in means).**	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10, eTable 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, eTable 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	eTable 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2-5, eFigures 1-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-12, 14, eTable 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-12, 14, eTables 2-3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

eProtocol

Protocol for a systematic review and meta-analysis on the associations between sensory impairments and frailty outcomes

Benjamin Kye Jyn Tan,[a*] Ryan Eyn Kidd Man,[b,c*] Alfred Tau Liang Gan,[b] Ecosse Luc Lamoureux[a,b,c]
a. Yong Loo Lin School of Medicine (YLLSoM), National University of Singapore (NUS), Singapore
b. Singapore Eye Research Institute (SERI), Singapore National Eye Centre (SNEC), Singapore
c. Duke-NUS Medical School, Singapore

Corresponding Author:
Professor Ecosse L. Lamoureux,
Singapore Eye Research Institute (SERI)
Director, Population Health
20 College Rd, The Academia
Discovery Tower Level 6, Singapore 169856
DID: (+65) 6576 7382
Email: ecosse.lamoureux@seri.com.sg

No existing protocols are available for this topic. This protocol is not registered. Deviations will be specified in the published manuscript for this systematic review and meta-analysis. This work is investigator-initiated and is not pending any specific funding.

Introduction

Frailty is a severe problem in the aged. With 54% of elders either frail or prefrail (1), and the world population of elders set to double by 2050 (2), frailty is a matter of public health concern. Though frailty was often dismissed as "normal ageing" just two decades ago (3), we now know that frailty is distinct from comorbidity, disability and ageing (4, 5). Crucially, frailty is reversible given appropriate interventions (6-8). In other words, growing old need not mean growing frail.

Naturally, much attention in recent years has been centered on the ways to slow, prevent or reverse frailty. While nutrition, physical activity, cognition and mood are well-established as risk factors for frailty (9-15), the relationship between sensory loss and frailty is uncertain. Sensory loss is a neglected but vital consideration because 94% of elderly have at least one sensory impairment, while two-thirds have two or more impairments (16). The special senses of vision, hearing, smell and taste are especially affected in elders due to a constellation of physiologic decline, multiple comorbidities and drug-related toxicity (17). If we could reduce the risk of frailty by correcting sensory loss, the cumulative impact could be enormous.

A sensory domain of frailty was first proposed two decades ago and interest was revived in recent years (18, 19). However, observational studies have garnered mixed results. To address this gap, we will conduct a systematic review and meta-analysis to examine the cross-sectional and longitudinal associations between various sensory impairments (vision, hearing, smell, taste) each with frailty.

Methods

This protocol was written with reference to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Ethical approval is not required as we will only conduct a secondary analysis of available data published in the literature. Our results will be submitted for peer-review publication and/or conference presentations.

Eligibility Criteria

Inclusion criteria:

1. Population: adults aged ≥55 years. We will include 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 (20, 21), 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 (e.g. Snellen chart, pure-tone audiometry) or validated subjective assessments (e.g. 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 (22) 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. We will accept other definitions of frailty and discuss the limitations of this approach.

5. Study type: observational studies (cross-sectional, longitudinal, and case-control) published as full-length articles or conference abstracts in peer-reviewed journals.

Exclusion criteria:

1. Specific sub-populations/special risk groups (e.g. individuals with cardiovascular disease).
2. Presence sensory impairment in the definition of frailty.
3. Disease-specific instead of sensory-specific associations (e.g. cataract or glaucoma instead of VI).
4. Failure to clearly distinguish between different types of sensory impairment.

We will not limit the searches by historical time constraints or language.

Information Sources

We will systematically search 3 databases (PubMed, Embase and the Cochrane Database of Systematic Reviews). We will also hand-search the bibliographies of included articles and relevant reviews or journals, where applicable. We will accept grey literature in the form of published poster abstracts if they are indexed in the above databases. We may attempt contact with the corresponding authors to obtain additional unpublished information such as (but not limited to) covariate-adjusted effect estimates.

Search Strategy

We will search PubMed, Embase and Cochrane using the following search strategy:

Free Text

#	Search Term
1	"vision" OR "visual" OR "sight" OR "seeing" OR "eyesight"
2	"hearing" OR "auditory" OR "audition" OR "aural"
3	"smell" OR "olfactory" OR "olfaction"
4	"taste" OR "gustatory" OR "gustation"
5	"sensory" OR "sensorial" OR "sensation"
6	"loss" OR "impairment" OR "dysfunction" OR "decline" OR reduc* OR decreas* OR diminish* OR difficult* OR problem* OR "trouble" OR "issues" OR deficit* OR deficien* OR insufficien* OR "hard" OR "poor" OR "bad" OR "low"
7	(1 OR 2 OR 3 OR 4 OR 5) AND 6
8	"blindness" OR "deafness" OR "presbycusis" OR "anosmia" OR "hyposmia" OR "microsmia" OR "ageusia" OR "hypogeusia"
9	7 OR 8
10	"frailty"
11	9 AND 10

Controlled Vocabulary: e.g. Medical Subject Headings (MeSH)

#	Search Term
1	("Vision Disorders"[MeSH]) AND "Frailty"[MeSH]
2	("Hearing Loss"[MeSH]) AND "Frailty"[MeSH]
3	("Ageusia"[MeSH] OR "Taste Disorders"[MeSH] OR "Taste Threshold"[MeSH] OR "Taste Perception"[MeSH]) AND "Frailty"[MeSH]
4	("Olfaction Disorders"[MeSH]) AND "Frailty"[MeSH]
5	("Sensation Disorders"[MeSH]) AND "Frailty"[MeSH]

Data Management

We will export the search results to EndNote or Microsoft Excel to remove duplicates and manually screen the records.

Selection Process

We will screen potentially eligible studies based on title and abstract, following which, we will retrieve full texts for evaluation. This will be done by 2 independent reviewers.

Data Extraction & Data Items

We will extract data from each article into a standardized extraction template. This data will include: 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. One reviewer will extract the data, and this will be verified by at least 1 other reviewer.

Risk of Bias

We plan to use the Newcastle-Ottawa Scale (NOS) (23), to evaluate the risk of bias at the outcome level. As per the NOS grading in past reviews, we will grade studies as having a high (<5 stars), moderate (5-7 stars) or low risk of bias (≥8 stars) (24-26).

Statistical Analysis

We will conduct all analyses using Stata, version 15.0 and will consider a 2-sided P value <0.05 as statistically significant for the purpose of these analyses. If we find sufficient data, we will meta-analyze the associations of various sensory impairments with frailty outcomes, including: (1) pre-frailty (vs. robustness), (2) frailty (vs. robustness), (3) frailty (vs. pre-frailty), (4) any frailty (i.e. combined pre-frailty/frailty). We will favor maximally covariate-adjusted estimates. If studies do not report an adjusted estimate due to stated insignificance, we will assume a null OR and estimate standard errors from a univariable logistic regression analysis of frequency counts, as previously described by Nicholson et al. (27) If studies use an analytical method that is incompatible for synthesis with the majority of other studies, we will calculate the unadjusted estimate from baseline frequency counts, to be included as a cross-sectional association. We will assess between-study heterogeneity using the Q-test or the I^2 statistic (28). We will use the random-effects model to synthesize study effects if significant heterogeneity is present (29). To study potential sources of study heterogeneity, we will perform univariable random-effects meta-regression analysis of various study-level characteristics: (1) frailty prevalence, (2) age [% aged ≥75], gender [% female], (3) covariate adjustment [yes vs. no], (4) race [Asian vs. Caucasian], (5) study design [cross-sectional vs. longitudinal], (6) risk of bias, (7) frailty definition [Fried vs. modified Fried or other criteria], (8) measure of impairment [objective/validated e.g. Snellen/audiometry/whisper test vs. self-report], (9) study setting [community vs. hospital-based]. We will repeat the meta-analyses in subgroups to explore the sensitivity of our results to study characteristics that are found to be significant effect modifiers. Finally, we will assess funnel plot asymmetry both visually and using Egger's bias test (30, 31). If we suspect publication bias, we will conduct a sensitivity analysis using the trim-and-fill method to re-estimate the pooled OR after imputing studies that are potentially missing (32).

References

1. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of Frailty in Community-Dwelling Older Persons: A Systematic Review. *Journal of the American Geriatrics Society*. 2012;**60**:1487-1492. doi: 10.1111/j.1532-5415.2012.04054.x
2. United Nations Department of Economic and Social Affairs. Key Findings and Advance Tables. In: World Population Prospects 2017, ed. New York: United Nations Secretariat; 2017.
3. Rockwood K, Hubbard R. Frailty and the geriatrician. *Age and ageing*. 2004;**33**:429-430. doi: 10.1093/ageing/afh153
4. Fried LP, Hadley EC, Walston JD, Newman AB, Guralnik JM, Studenski S, *et al.* From bedside to bench: research agenda for frailty. *Science of aging knowledge environment : SAGE KE*. 2005;**2005**:pe24. doi: 10.1126/sageke.2005.31.pe24
5. Walston J. Frailty--the search for underlying causes. *Science of aging knowledge environment : SAGE KE*. 2004;**2004**:pe4. doi: 10.1126/sageke.2004.4.pe4
6. Apostolo J, Cooke R, Bobrowicz-Campos E, Santana S, Marcucci M, Cano A, *et al.* Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: a systematic review. *JBI database of systematic reviews and implementation reports*. 2018;**16**:140-232. doi: 10.11124/jbisrir-2017-003382
7. Rodríguez Monforte M, Toubasi S, Puts MTE, Andrew MK, Ashe MC, Ploeg J, *et al.* Interventions to prevent or reduce the level of frailty in community-dwelling older adults: a scoping review of the literature and international policies. *Age and ageing*. 2017;**46**:383-392. doi: 10.1093/ageing/afw247
8. Lang PO, Michel JP, Zekry D. Frailty Syndrome: A Transitional State in a Dynamic Process. *Gerontology*. 2009;**55**:539-549. doi: 10.1159/000211949
9. Manal B, Suzana S, Singh DK. Nutrition and Frailty: A Review of Clinical Intervention Studies. *The Journal of frailty & aging*. 2015;**4**:100-106. doi: 10.14283/jfa.2015.49
10. Lorenzo-López L, Maseda A, de Labra C, Regueiro-Folgueira L, Rodríguez-Villamil JL, Millán-Calenti JC. Nutritional determinants of frailty in older adults: A systematic review. *BMC geriatrics*. 2017;**17**:108-108. doi: 10.1186/s12877-017-0496-2
11. Hernández Morante JJ, Gómez Martínez C, Morillas-Ruiz JM. Dietary Factors Associated with Frailty in Old Adults: A Review of Nutritional Interventions to Prevent Frailty Development. *Nutrients*. 2019;**11**. doi: 10.3390/nu11010102

12. Vaughan L, Corbin AL, Goveas JS. Depression and frailty in later life: a systematic review. *Clinical interventions in aging*. 2015;**10**:1947-1958. doi: 10.2147/cia.S69632
13. Brigola AG, Rossetti ES, Dos Santos BR, Neri AL, Zazzetta MS, Inouye K, *et al.* Relationship between cognition and frailty in elderly: A systematic review. *Dementia & neuropsychologia*. 2015;**9**:110-119. doi: 10.1590/1980-57642015dn92000005
14. Silva RB, Aldoradin-Cabeza H, Eslick GD, Phu S, Duque G. The Effect of Physical Exercise on Frail Older Persons: A Systematic Review. *The Journal of frailty & aging*. 2017;**6**:91-96. doi: 10.14283/jfa.2017.7
15. Fried LP. Interventions for Human Frailty: Physical Activity as a Model. *Cold Spring Harbor perspectives in medicine*. 2016;**6**. doi: 10.1101/cshperspect.a025916
16. Correia C, Lopez KJ, Wroblewski KE, Huisingh-Scheetz M, Kern DW, Chen RC, *et al.* Global Sensory Impairment in Older Adults in the United States. *Journal of the American Geriatrics Society*. 2016;**64**:306-313. doi: 10.1111/jgs.13955
17. Lanska DJ. Disorders of the Special Senses in the Elderly. In: Nair AK, Sabbagh MN, eds. Geriatric Neurology. John Wiley & Sons, Ltd; 2014.
18. Strawbridge WJ, Shema SJ, Balfour JL, Higby HR, Kaplan GA. Antecedents of frailty over three decades in an older cohort. *The journals of gerontology Series B, Psychological sciences and social sciences*. 1998;**53**:S9-16.
19. Panza F, Lozupone M, Sardone R, Battista P, Piccininni M, Dibello V, *et al.* Sensorial frailty: age-related hearing loss and the risk of cognitive impairment and dementia in later life. *Therapeutic Advances in Chronic Disease*. 2018:2040622318811000. doi: 10.1177/2040622318811000
20. Griffin FR, Mode NA, Ejiogu N, Zonderman AB, Evans MK. Frailty in a racially and socioeconomically diverse sample of middle-aged Americans in Baltimore. *PloS one*. 2018;**13**:e0195637. doi: 10.1371/journal.pone.0195637
21. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of Frailty in Middle-Aged and Older Community-Dwelling Europeans Living in 10 Countries. *The Journals of Gerontology: Series A*. 2009;**64A**:675-681. doi: 10.1093/gerona/glp012
22. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, *et al.* Frailty in older adults: evidence for a phenotype. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2001;**56**:M146-156.
23. GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell,. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2012.
24. Kojima G, Avgerinou C, Iliffe S, Walters K. Adherence to Mediterranean Diet Reduces Incident Frailty Risk: Systematic Review and Meta-Analysis. *Journal of the American Geriatrics Society*. 2018;**66**:783-788. doi: 10.1111/jgs.15251
25. Saraiva MD, Suzuki GS, Lin SM, de Andrade DC, Jacob-Filho W, Suemoto CK. Persistent pain is a risk factor for frailty: a systematic review and meta-analysis from prospective longitudinal studies. *Age and ageing*. 2018;**47**:785-793. doi: 10.1093/ageing/afy104
26. Vetrano DL, Palmer KM, Galluzzo L, Giampaoli S, Marengoni A, Bernabei R, *et al.* Hypertension and frailty: a systematic review and meta-analysis. *BMJ Open*. 2018;**8**:e024406. doi: 10.1136/bmjopen-2018-024406
27. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006;**27**:2763-2774. doi: 10.1093/eurheartj/ehl338
28. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine*. 2002;**21**:1539-1558. doi: 10.1002/sim.1186
29. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*. 1986;**7**:177-188.
30. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;**50**:1088-1101.
31. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)*. 1997;**315**:629-634. doi: 10.1136/bmj.315.7109.629
32. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;**56**:455-463.