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Review

Multimorbidity and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies

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ABSTRACT

Background: Chronic diseases (e.g., hypertension, diabetes, and heart diseases) have been proposed as marked predictors of incident dementia. However, synthesised evidence on the effect of multimorbidity on dementia is still lacking. We aim to summarise the association between multimorbidity and risk of dementia in longitudinal cohorts.

Methods: In this systematic review and meta-analysis, we conducted a systematic search in PubMed, Web of Science and Embase from inception to Dec 14, 2024, to identify longitudinal cohort studies reporting the association between multimorbidity or multimorbidity patterns and risk of dementia. Information of included studies were extracted by three reviewers (YaZ, YY and YuZ), and the quality assessment was conducted using the Newcastle-Ottawa Scale. The inverse-variance weighted random effects meta-analysis was performed to obtain the pooled hazard ratios (HRs) and 95 % confidence intervals (CIs) for dementia associated with multimorbidity and cardiometabolic multimorbidity (CMM). Cochran's Q test and the I^2 statistic were used to indicate heterogeneity among the studies. Meta-regression analysis, subgroup analysis and sensitivity analysis were conducted to determine any valid sources of heterogeneity. This study was registered with PROSPERO (CRD42023403684).

Results: We included 17 longitudinal cohort studies (2262,885 middle-aged and older participants) in the systematic review, of which seven were included in meta-analysis. All studies presented moderate to high methodological quality. Meta-analysis showed a positive association between multimorbidity and incident dementia (HR=1.53, 95 % CI=1.12 to 2.09), with substantial heterogeneity (I^2=95.2 %). Studies using health records to measure dementia tend to find a stronger positive relationship between multimorbidity and risk of dementia than those using self-report ($HR_{\text{health records}}$=1.94, 95 % CI=1.35 to 2.78, I^2=94 %; $HR_{\text{self-report}}$=1.17, 95 % CI=1.07 to 1.28, I^2=0 %). The impacts of CMM were also observed, and the HRs for dementia ranged from 2.49 (combination of heart diseases and stroke: 95 % CI=1.64 to 3.78) to 3.77 (combination of diabetes, heart diseases and stroke: 95 % CI=2.02 to 7.02). The heterogeneity was moderate, with I^2 ranging from 46.9 % (p for heterogeneity=0.152) to 84.1 % (p for heterogeneity=0.002). The impacts of number of diseases, multimorbidity clusters, and multimorbidity trajectory on risk of dementia were narratively summarised due to lacking comparable studies. Limited evidence (only one study) precluded quantitative synthesis for the association of physical and psychological multimorbidity with dementia.

Conclusion: Multimorbidity and CMM pattern were significantly associated with risk of dementia, while the effect of physical and psychological multimorbidity remain inconclusive. Individuals affected by multimorbidity should be prioritised in risk factor modification and dementia prevention. Preventing the development of multimorbidity is also crucial—particularly those who already have one chronic disease—in order to maintain cognitive health.

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1. Introduction

Dementia, a clinical syndrome resulting from neurodegenerative conditions, is a huge and persistent challenge faced by individuals and societies [1]. The number of people with dementia is projected to increase 3 fold from 57.4 million cases in 2019 to 152.8 million cases by 2050 [2]. Dementia subtypes, especially Alzheimer's disease (AD) and vascular dementia (VaD), were also estimated to affect a growing population [3]. As one of the most expensive, lethal and burdening diseases of this century, dementia leads to many adverse health outcomes, including functional limitations, dependency, disability and mortality [4]. Due to the absence of curative drugs and effective medical treatments, identification of early signs and relevant interventions is critical for dementia prevention [5].

In the context of population aging and advanced modern medicine, the prevalence of chronic diseases (e.g., diabetes, cancer, heart diseases and psychological disorders) increased globally, causing the coexistence of chronic diseases, called multimorbidity [6]. The epidemiology of multimorbidity followed an S-shape pattern with aging, presenting another inevitable public health concern [6]. Specifically, cardiometabolic multimorbidity, defined as the coexistence of diabetes, heart diseases and stroke, was one of the most replicable multimorbidity profiles, according to a previous systematic review [7]. In addition, the strong interlinking between physical and psychological chronic conditions has highlighted the importance of identifying physical and psychological multimorbidity [8].

Previous systematic reviews and meta-analyses have summarised how and to what extent chronic diseases predict dementia. For example, patients with diabetes were found to have a higher incidence of dementia than those without diabetes [9]. A previous meta-analysis including 48 studies concluded that stroke, either prevalent or incident, was related to 69 % to 118 % higher risk of all-cause dementia, despite with substantial heterogeneity [10]. A significantly increased risk of VaD was found in patients with hypertension, stressing the potential importance of hypertension management in dementia prevention strategies [11]. After collating 51 case-control and cohort studies, Joaquim da Silva et al. revealed the positive association between affective disorders and risk of dementia, suggesting that depression might be both a prodrome and a risk factor [12]. Since cumulative reliable evidence unveiled the association between several chronic diseases and dementia, emerging longitudinal research has directed considerable attention to multimorbidity and multimorbidity patterns as risk factors of dementia. However, no systematic attempt had been made to synthesise findings from studies of the association between multimorbidity and incident dementia. Therefore, the aim of this systematic review and meta-analysis is to examine and synthesise the association of multimorbidity and specific multimorbidity patterns with dementia in longitudinal cohorts, as well as to find potential effect modifiers.

2. Methods

2.1. Systematic search and study selection

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [13]. The present study was registered in the international prospective register of systematic reviews (PROSPERO) under the protocol number: CRD42023403684. A systematic database search in PubMed, Web of Science and Embase was conducted from inception to Dec 14, 2024, with an English-language restriction. Search strings included terms on (1) multimorbidity (e.g., multimorbidity, multiple chronic diseases, coexisting diseases, cardiometabolic multimorbidity) and (2) dementia (e.g., dementia; Alzheimer's disease, memory disorder, cognitive decline). Details of the searching strategy are included in **Supplementary Table S1-S3**. Reference lists of all included studies and relevant reviews on this topic were also manually screened.

Two reviewers (YaZ and YY) independently screened the title and abstract of selected studies and further read the full text for inclusion. Studies were included if they (1) were published in a peer-reviewed journal; (2) used a longitudinal cohort study design among adults; and (3) reported on an association between multimorbidity or multimorbidity patterns and risk of dementia in a quantitative way. Any disagreements were resolved through consultation with a third investigator (YuZ).

2.2. Data extraction and methodological quality assessment

Three reviewers (YaZ, YY and YuZ) independently extracted the following information from each study using pre-designed data extraction forms: first author, year of publication, journal, database, sample size, the proportion of females, population age, follow-up duration, multimorbidity measurement, dementia assessment, effect sizes, covariates and main results. Any disagreement between the reviewers regarding the data extraction process was resolved through discussion with XX.

The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality of cohort studies by the same reviewers (**Supplementary Table S4**). The NOS allocates a maximum of nine points for the quality of study selection (0–4 points), the comparability of the groups (0–2 points), and the ascertainment of the outcome (0–3 points) [14]. Cohort studies with points of 0–3, 4–6 and 7–9 were deemed as low, moderate and high quality, respectively. Any discrepancies were resolved in consensus.

2.3. Statistical analysis

Descriptive statistics of included studies were summarised, according to multimorbidity [15–25] and two multimorbidity patterns: CMM [26–30] and physical and psychological multimorbidity [31]. Due to the expected heterogeneity, the random effects meta-analysis was performed to obtain the pooled hazard ratios (HRs) and confidence intervals (CIs) for incident dementia from models adjusting most available covariates in each study. The generic inverse variance method was used, in which studies with a more precise estimate of the effect size have low variance and are assigned more weight, and those with a less precise estimate of the effect size have high variance and are assigned less weight [32]. Studies using the same definition of multimorbidity and with comparable statistical results were included in the meta-analysis [15–17,25], and the remaining studies were narratively described. As several studies reported Alzheimer's disease and vascular dementia as secondary outcomes, we also summarised the impact of multimorbidity on them. Similarly, studies using the same combinations of CMM and with comparable statistical results were included in the meta-analysis [26,28,29]. Cochran's Q test and the I^2 statistic were used to indicate heterogeneity among the studies, with the former considering $p < 0.05$ as significant for heterogeneity, and the latter having cut-offs of 50 %, and 75 % for low, medium, and high heterogeneity, respectively [33]. Meta-regression analysis and subgroup analysis were conducted to determine any valid sources of heterogeneity and find potential modifiers. Mean/median age, country, sample size, follow-up years, multimorbidity measurement, and dementia measurement were included in the meta regression analysis as the independent variables. Sensitivity analyses were further conducted by a leave-one-out procedure for the associations of multimorbidity and CMM with dementia, respectively. Visual inspection of funnel plots and the Egger's regression test were used to assess publication bias. Indications of publication bias was gauged by inspecting a funnel plot, which allows distinguishing asymmetry due to publication bias from other factors by including areas of statistical significance on the funnel plot [34]. We also used Egger's regression test as objective measures of funnel plot asymmetry [35].

All analyses were performed in R (Version 4.2.2) and Stata MP (version 17.0).

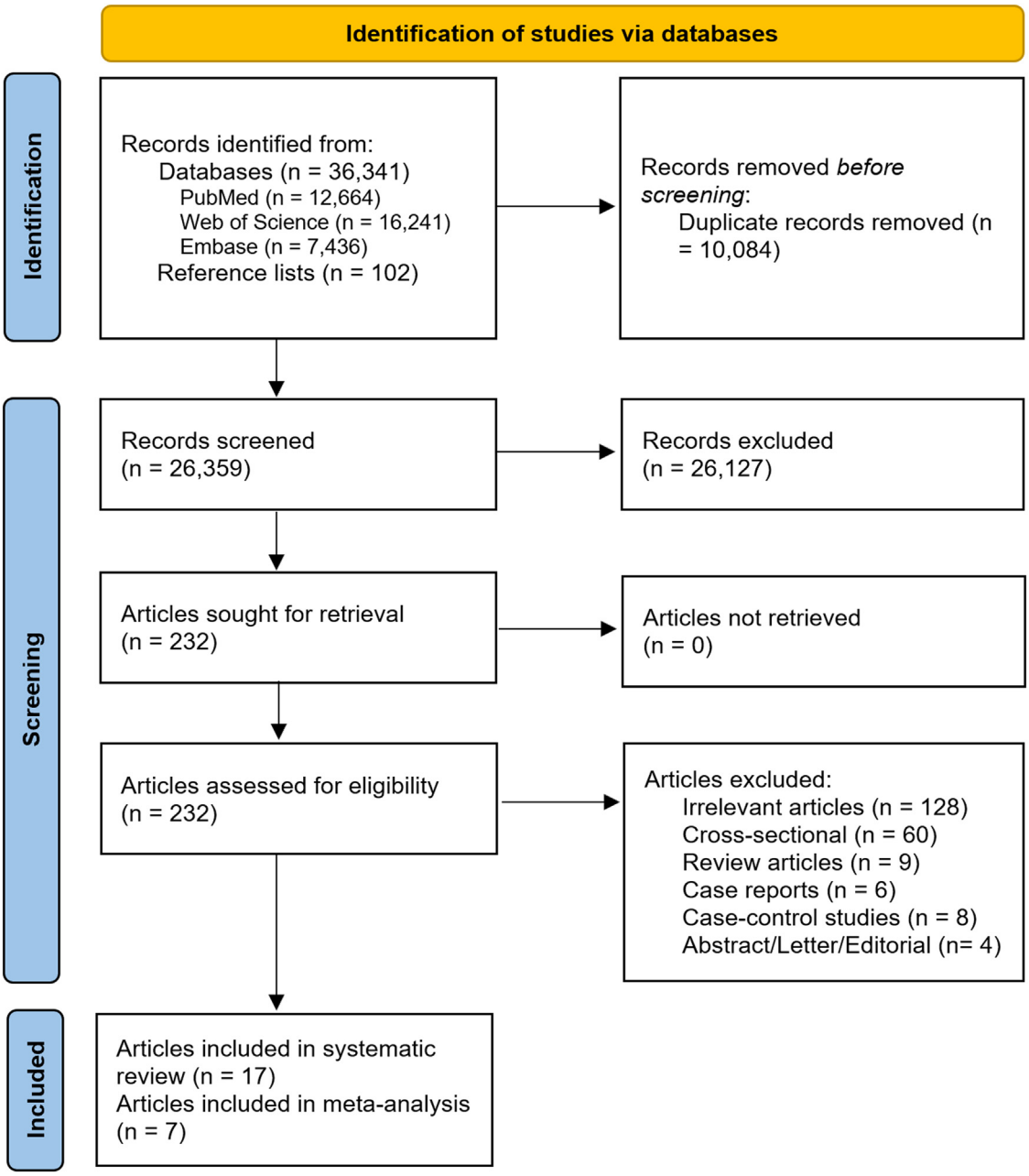

Fig. 1. Flowchart of study selection.

3. Results

3.1. Literature search

The initial search yielded 36,341 studies from the databases and 102 studies from reference lists. After removal of duplicates and screening titles and abstracts, 232 were selected for full-text review. According to the eligible criteria, 17 longitudinal cohort studies were finally included [15–31] of which 7 were included in meta-analysis [15–17,25,26,28,29] (Fig. 1).

3.2. Characteristics of included systematic reviews

Detailed characteristics of included studies are presented in Table 1. All included studies were published in recent five years, comprising a total of 2262,885 participants. The sample size of each study ranged from 704 [27] to 471,485 [23], and nearly half used individual data from UK Biobank [16,20–23,28,30]. The majority of studies were conducted in the general older adult population [16,17,19,20,25,26,28–31], four studies also included middle-aged adults [15,21–23]. The studies of Grande et al. and Valletta et al. solely focused on older adults with two or more chronic diseases to identify different multimorbidity clusters [18,24], and the study of Dove et al. reported the risk of dementia in older adults with baseline cognitive impairment [27]. The duration of follow-up varied between 6.0 [31] to 31.7 years [15]. According to the NOS, eight studies presented high methodological quality [15,17,20,22,23,26,28,29], and the remaining nine presented moderate. More details on quality assessment can be found in Table 2.

The information on multimorbidity was collected by self-report [16,17,19,22,25,31], health records or clinical examinations [15,20,21,29], or combined approaches [18,23,24,26–28,30]. Most studies collected the information on dementia by health records or

Table 1
Characteristics of cohort studies of the association between multimorbidity and risk of dementia.

Author, year	Database	Sample (%female)	Mean age (SD)/median age (IQR), years	Mean/median follow-up years	Multimorbidity definition	Multimorbidity measurement	Dementia type	Dementia measurement	Main results
Multimorbidity and dementia									
Ben Hassen et al., 2022 [15]	Whitehall II study	10,095 (32.7)	Mean 44.9 (NA)	Median 31.7	Multimorbidity: ≥2 diseases out of 13 chronic diseases	Clinical examinations; linkage to electronic health records	All-cause dementia	Health records	Multimorbidity, particularly when onset is in midlife rather than late life, has a robust association with subsequent dementia.
Calvin et al., 2022 [16]	UKB	206,960 (52.7)	Mean 64.1 (2.9); 52.7 %	Mean 11.8	Multimorbidity: ≥2 diseases out of 42 chronic diseases Multimorbidity cluster: hypertension, diabetes, and CHD; cancer; thyroid; pain, dyspepsia, and depression; asthma and COPD; pain and hypertension; pain, osteoporosis, and dyspepsia; hypertension, pain, and dyspepsia; CHD, hypertension, and stroke; asthma, COPD, and psoriasis; pain, dyspepsia, and prostate disorders; diabetes, hypertension, and cancer	Self-report	All-cause dementia	Health records	Multimorbidity was associated with an increased risk of dementia.
Chen et al., 2022 [17]	HRS	5923 (58.6)	Mean 73.6 (6.8)	Median 8	Multimorbidity: ≥2 diseases out of 8 chronic diseases) Number of chronic diseases: 0 or 1, 2, 3, 4, ≥5. Multimorbidity trajectory: rapid growth; steady growth; slow growth; and no new condition	Self-report	All-cause dementia, AD, other types of dementia	Self-report	Compared to individuals with zero or one chronic condition, those with two or more conditions had a higher risk of incident dementia.
Grande et al., 2021 [18]	SNAC-K	2478 (64.3)	Mean 75.0 (10.4)	Mean 8.4	Multimorbidity patterns out of 35 diseases: neuro-psychiatric; cardiovascular; sensory impairment/cancer; respiratory/metabolic/ musculoskeletal; unspecific	Physical examination, self-report and health records	All-cause dementia	Clinical diagnosis (DSM-IV), and health records	Individuals with neuropsychiatric, cardiovascular, and sensory impairment/cancer patterns are at increased risk for dementia.
Guo et al., 2023 [19]	HRS	7008 (48.0)	Mean 74.1 (7.5)	Mean 12.8	Multimorbidity: ≥2 diseases out of 7 chronic diseases	Self-report	All-cause dementia	Cognitive test	The faster accumulation of multimorbidity in prodromal dementia than in natural aging.

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Table 1 (*continued*)

Author, year	Database	Sample (%female)	Mean age (SD)/median age (IQR), years	Mean/median follow-up years	Multimorbidity definition	Multimorbidity measurement	Dementia type	Dementia measurement	Main results
Hu et al., 2022 [20]	UKB	245,483 (53.2)	Mean 62.3 (4.1)	Median 9.26	Multimorbidity patterns: obesity accompanied with other disorders; cardio-cerebrovascular/respiratory/ metabolic/musculoskeletal/ depressive disorders; tu-mor/genitourinary/digestive disorders	Health records	All-cause dementia, AD, VD	Health records	Participants with multimorbidity at baseline had higher risks of all-cause dementia and VD, and the risks were elevated with the increase of long-term conditions counts.
Khondoker et al., 2023 [21]	UKB	447,888 (54.3)	Median 58.0 (13.0)	Median 11.3	Multimorbidity patterns out of 27 diseases: inflammation dominated; mental health dominated; cardiometabolic dominated; and cancer dominated	Health records	All-cause dementia	Health records	People living with cardiometabolic, mental health, inflammation and cancer clusters of multimorbidity appear to be more likely to develop dementia as people without multimorbidity.
Niu et al., 2024 [22]	UKB	428,924 (53.3)	Mean 56.4 (8.1)	Median 12.5	Number of chronic diseases: 0 or 1, 2, ≥3. Multimorbidity types: cardiovascular diseases; metabolic diseases; neuro-psychiatric diseases; inflammation-related diseases	Self-report	All-cause dementia, AD, VD	Health records	Multimorbidity including cardiovascular, metabolic, neuropsychiatric, and inflammation-related diseases was associated with a higher risk of subsequent dementia.
Shang et al., 2022 [23]	UKB	471,485 (54.5)	Mean 56.8 (8.0)	Median 11.9	Number of chronic diseases (out of 62 chronic diseases): 0, 1, 2, 3, 4, 5, ≥6.	Self-report and health records	All-cause dementia, AD, VD	Health records	Individual diseases and multimorbidity are strong predictors of dementia.
Valletta et al., 2023 [24]	SNAC-K	3122 (63.4)	Mean 73.6 (10.7)	About 18	Multimorbidity patterns out of 37 chronic diseases: neuropsychiatric; cardiovascular; cancer/sensory impairment; respiratory/musculoskeletal/ metabolic; unspecific	Physical examination, self-report and health records	All-cause dementia	Clinical diagnosis (DSM-IV), and health records	Multimorbidity patterns have an impact on dementia development.

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Table 1 (*continued*)

Author, year	Database	Sample (%female)	Mean age (SD)/median age (IQR), years	Mean/median follow-up years	Multimorbidity definition	Multimorbidity measurement	Dementia type	Dementia measurement	Main results
Veronese et al., 2023 [25]	SHARE	23,196 (56.2)	Mean 64.3 (10.1)	About 15	Multimorbidity: ≥2 diseases out of 14 chronic diseases	Self-report	All-cause dementia	Self-report	Multimorbidity significantly increases the risk of dementia, particularly in younger people.
CMM and dementia									
Dove et al., 2023a [26]	Swedish Twin Registry	17,913 (55.0)	Mean 70.1 (7.5)	Median 15.4	CMM combinations out of type 2 diabetes, heart disease, and stroke	Self-report, records from the NPR, and medication information	All-cause dementia, AD, VD	Records from the NPR and the Swedish Cause of Death Register	CMM, particularly in mid-life, is associated with an increased risk of dementia.
Dove et al., 2023b [27]	SNAC-K	704 (67.3)	Mean 76.0 (NA)	Median 7.0	CMM combinations out of type 2 diabetes, heart disease, and stroke Number of CMDs	Self-report, records from the NPR, and medication information	All-cause dementia	Clinical diagnosis (DSM-IV), and health records	CMM accelerates cognitive decline and increases the risk of conversion to dementia.
Tai et al., 2022 [28]	UKB	203,038 (52.8)	Mean 64.9 (3.0)	Median 12	CMM combinations out of stroke, myocardial infarction, and diabetes Number of CMDs	Self-report and health records	All-cause dementia, AD, other dementia	Health records	CMM was independently associated with the risk of dementia.
Wang et al., 2020 [29]	SNAC-K	2648 (63.0)	Mean 73.6 (10.5)	Median 11.0	CMM combinations out of stroke, myocardial infarction, and diabetes Number of CMDs	Physical examination and health records	All-cause dementia	Cognitive test and health records	CMDs were associated with increased dementia risk, and the risk was dose-dependently related to the number of CMDs.
Xiong et al., 2023 [30]	UKB	171,538 (51.5)	Mean 64.1 (2.8)	Median 12.3	CMM combinations out of hypertension, type 2 diabetes, CHD, and stroke Number of CMDs	Self-report and health records	All-cause dementia	Health records	The presence of CMDs was dose-dependently associated with an increased risk of dementia.
Physical and psychological multimorbidity and dementia									
Du et al., 2024 [31]	HRS, SHARE	HRS: 8543 (58.3); SHARE: 5939 (42.3)	Median 71.0 (13.0)	About 6	Multimorbidity: the presence of physical (any of seven chronic diseases) and psychological disorders (CES-D score ≥4)	Self-report	All-cause dementia	Self-report and cognitive tests	The risk of dementia increased among participants who reported physical and psychological multimorbidity in various cohorts.

SD, standard deviation; IQR, Interquartile range; NA, not available; UKB, UK Biobank; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; HRS, US Health and Retirement Study; AD, Alzheimer's disease; SHARE, The Survey of Health, Ageing and Retirement in Europe; CES-D, Center for Epidemiologic Studies Depression Scale; SNAC-K, Swedish National study on Aging and Care in Kungsholmen; DSM-IV, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders; VD, vascular dementia; CMM, cardiovascular multimorbidity; NPR, National Patient Register.

Table 2
The quality assessment for cohort studies.

Study	Quality score			Total score	Quality
	Selection	Comparability	Outcome		
Multimorbidity and dementia					
Ben Hassen et al., 2022 [15]	4	2	3	9	High
Calvin et al., 2022 [16]	3	1	2	6	Moderate
Chen et al., 2022 [17]	3	2	2	7	High
Grande et al., 2021 [18]	3	1	1	5	Moderate
Guo et al., 2023 [19]	3	1	1	5	Moderate
Hu et al., 2022 [20]	3	2	2	7	High
Khondoker et al., 2023 [21]	3	1	2	6	Moderate
Niu et al., 2024 [22]	3	2	3	8	High
Shang et al., 2022 [23]	3	1	2	7	High
Valletta et al., 2023 [24]	2	1	1	4	Moderate
Veronese et al., 2023 [25]	3	1	2	6	Moderate
CMM and dementia					
Dove et al., 2023a [26]	4	2	3	9	High
Dove et al., 2023b [27]	2	1	1	4	Moderate
Tai et al., 2022 [28]	3	1	3	7	High
Wang et al., 2020 [29]	3	2	2	7	High
Xiong et al., 2023 [30]	2	2	1	5	Moderate
Physical and psychological multimorbidity and dementia					
Du et al., 2024 [31]	3	1	1	5	Moderate

CMM, cardiovascular diseases.

cognitive tests, two by self-report [17,25], and one by combined approaches [31]. The majority of studies reported quantitatively or qualitatively on the association between multimorbidity and incident dementia (n = 11) [15–25]. Of these, several studies regarded AD (n = 4) [17,20,22,23] and VaD (n = 3) [20,22,23] as secondary outcomes. The chronic diseases for constructing multimorbidity ranged from 7 [19] to 62 [23]. Four of these studies defined multimorbidity as the coexistence of ≥2 chronic diseases [15–17,25], six counted the number of coexisting chronic diseases, five identified multimorbidity clusters using either a fuzzy c-means cluster analysis algorithm [18,20,24] or latent class analysis [16,21], and two studies evaluated multimorbidity trajectory by group-based trajectory modelling [17] or mixed-effects models [19]. Five studies reported on the association between CMM and incident dementia, and all of them included three cardiometabolic diseases (CMDs): type 2 diabetes, heart diseases and stroke [26–30] excepting one additionally included hypertension [30]. All these studies evaluated specific CMM combinations, and four studies also evaluated the number of CMDs [27–30]. Only one study reported the association between physical and psychological multimorbidity and incident dementia, and those with any of seven chronic disease and an 8-item CES-D score greater than 3 were regarded as having physical and psychological multimorbidity [31].

3.3. Multimorbidity and risk of dementia

Eleven studies examined the association between multimorbidity and incident dementia, of which four defining multimorbidity status as the coexistence of ≥2 chronic diseases were included in the meta-analysis. Data pooled from the studies showed a significant positive association between multimorbidity and incident dementia (HR=1.53, 95 % CI=1.12 to 2.09, Fig. 2), exhibiting substantial between-study heterogeneity (p for heterogeneity <0.001, I^2=95.2 %). Meta-regression analysis did not find significant modifiers for the association (Table 3), while subgroup analysis showed that studies using health records to measure dementia tend to find a stronger positive relationship between multimorbidity and risk of dementia than those using self-report ($HR_{self\text{-}report}$=1.17, 95 % CI=1.07 to 1.28, p for heterogeneity=0.34, I^2=0 %; $HR_{health\ records}$=1.94, 95 % CI=1.35 to 2.78, p for heterogeneity <0.001, I^2=94 %; Table 4). The leave-one-out procedure did not reveal any overly influential study, while the 95 % CI widened to non-significant when excluding the study of Calvin et al. [16] (Table 4). Funnel plots and Egger's regression test indicated no significant publication bias for the association between multimorbidity and risk of dementia (t = 2.09, p = 0.172) (Table 5, **Supplementary Figure S1**).

Six studies reporting the dose-response relationship between number of chronic diseases and dementia were not included in the meta-analysis, due to different diseases range and reference groups. However, all these studies observed that a higher number of chronic diseases contributed to a higher risk of dementia [15–17,20,22,23]. Five studies identified different multimorbidity clusters using either a fuzzy c-means cluster analysis algorithm or latent class analysis. The study of Calvin et al. found the dementia risk was highest for hypertension, diabetes, and coronary heart disease cluster in women, and diabetes and hypertension cluster in men [16]. The study of Hu et al. of 245,483 participants aged ≥60 years reported a 14 % to 46 % times the risk of dementia in multimorbidity clusters than the multimorbidity-free group [20], and the study of Niu et al. of a doubled sample size found 36 % to 112 % times the risk of dementia [22]. The study of Grande et al. grouped 2478 participants with multimorbidity into different patterns, and found that individuals with neuropsychiatric, cardiovascular, and sensory impairment/cancer patterns were at increased risk for dementia compared to the unspecific pattern [18], while another study reported that participants with the cardiovascular pattern experienced a higher risk of progression from cognitive impairment to dementia than the unspecific pattern [24]. In addition, the study of Guo et al. reported that the trajectory of multimorbidity increased faster in prodromal dementia than in natural aging [19], which was supported by another study using data from the US [17].

We also summarised the risk of AD and VaD as secondary outcomes associated with multimorbidity. A study of older adults in the US reported that the multimorbidity group experienced 10 % times the risk of AD [17]. The study of Hu et al. found that the HR of AD ranged from 1.07 (95 % CI=0.91 to 1.25) to 1.28 (95 % CI=1.04 to 1.58), and that of VaD ranged from 1.54 (95 % CI=1.11–2.14) to 1.73(95 % CI=1.37–2.18) in different multimorbidity clusters [20]. The dose-response relationships between number of chronic diseases with AD and VaD were observed in those studies of UK participants, with a larger association strength occurring in VaD [22,23].

3.4. Cardiometabolic multimorbidity and risk of dementia

Five studies examining the association between CMM and incident dementia, and three of them using the same diseases to construct CMM were included in the meta-analysis. As shown in Fig. 3, a dose-dependent

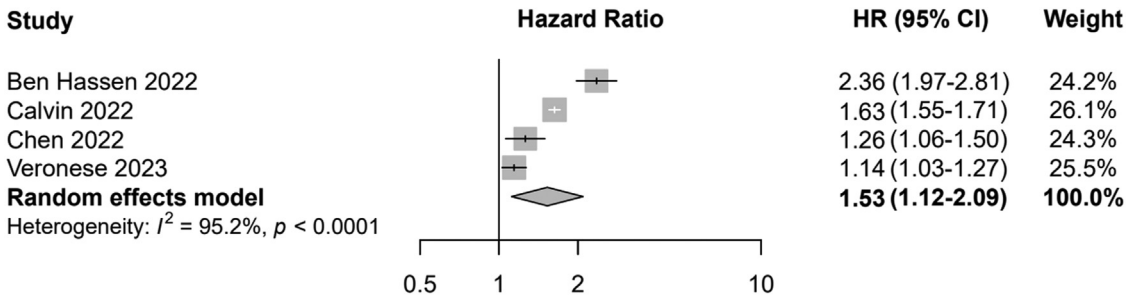

Fig. 2. Meta-analysis of the impact of multimorbidity on risk of dementia in the adjusted model.
HR, hazard ratio; CI, confidence interval.

Table 3
Meta-regression of effect modifiers of multimorbidity on risk of dementia.

Modifier	β (95 % CI)	p value	R^2	τ^2
Mean/median age, years				
<60	Ref			
≥60	-0.391 (-1.918, 1.135)	0.385	8.13 %	0.088
Country				
US	Ref			
UK	0.431 (-3.687, 4.550)	0.410	34.10 %	0.063
European countries*	-0.098 (-4.811, 4.615)	0.835		
Sample size				
<100 000	Ref			
≥100 000	0.085 (-1.836, 2.006)	0.867	−52.58 %	0.147
Follow-up years				
<10	Ref			
≥10	-0.125 (-1.776, 1.525)	0.775	−47.23 %	0.142
Multimorbidity measurement				
Self-report	Ref			
Examination/Health records	0.566 (-0.439, 1.571)	0.136	64.77 %	0.034
Disease range#				
<20	Ref			
≥20	-0.566 (-1.571, 0.439)	0.136	64.77 %	0.034
Dementia measurement				
Self-report	Ref			
Health records	0.475 (-0.351, 1.301)	0.132	66.47 %	0.032

CI, confidence interval.
* : Excluding UK.
# : Numbers of chronic diseases used to construct multimorbidity.

association between the number of CMDs and risk of dementia was observed. Each CMD was associated with a higher risk of incident dementia, with HRs of 1.59 (95 % CI=1.13–2.25) for diabetes, 1.45 (95 % CI=1.25–1.69) for heart diseases, and 1,88 (95 % CI=1.58–2.24) for stroke respectively. The positive association between CMM combinations and incident dementia was also observed, and the pooled HRs were 2.69 (95 % CI=1.99 to 3.63) in diabetes and heart diseases, 2.49 (95 % CI=1.64 to 3.78) in heart diseases and stroke, 3.01 (95 % CI=1.69–5.35) in diabetes and stroke, and 3.77 (95 % CI=2.02–7.02) in diabetes, heart diseases and stroke. The heterogeneity was moderate, with I^2 ranging from 46.9 % (p for heterogeneity=0.152) to 84.1 % (p for heterogeneity=0.002). No meta-regression analysis and subgroup analysis were conducted due to the limited number of comparable studies. In the combinations of diabetes and heart diseases, and diabetes, heart diseases and stroke, the leave-one-out procedure by excluding the study of Dove et al.(a) reduced the heterogeneity to non-significant, while the study of Tai et al. was an overly influential study for another two CMM combinations (**Supplementary Table S5**). Funnel plots and Egger's regression test indicated no evidence on publication bias (t = 1.25 to 5.88, p = 0.107 to 0.430) (Table 5**, Supplementary Figure S2**). The study of Xiong et al. additionally included hypertension in CMM and also reported the positive associations between CMM combinations and risk of dementia. The study of Dove et al. (b) focused on the cognitive impaired participants and only found significantly higher risk of dementia in the combination of diabetes, heart diseases and stroke.

Four studies reporting the dose-response relationship between number of CMDs and dementia were not included in the meta-analysis, due to different diseases range and reference groups. However, all these studies observed that a higher number of CMDs contributed to a higher risk of dementia [27–30].

3.5. Physical and psychological multimorbidity and risk of dementia

The study of Du et al. included 14,482 adults aged ≥50 years from Europe and US and examined the association of physical and psychological multimorbidity with risk of dementia. The fully adjusted model showed that compared to those with no physical or psychological disorders, the HR of incident dementia was 1.86 (95 % CI=1.08 to 3.21) in Europe and 2.76 (95 % CI=1.61 to 4.72) in the US among participants with physical and psychological multimorbidity.

4. Discussion

In this systematic review of 17 cohort studies, we summarised evidence on the longitudinal association of multimorbidity and multimorbidity patterns with risk of dementia. Results from meta-analysis showed that multimorbidity are associated with 1.53 times higher the risk of dementia, while the HRs of CMM combinations ranged from 2.49 to 3.77. Heterogeneity between results for multimorbidity and CMM with dementia, however, limits the interpretability of these outcomes. The

Table 4
Summary of subgroup and sensitivity analysis for multimorbidity and risk of dementia.

	Articles (n)	Pooled HR (95 % CI)	Heterogeneity	
			p	I^2 (%)
Subgroup analysis				
Mean/median age, years				
<60	1	2.36 (1.97, 2.81)	NA	NA
≥60	3	1.33 (1.03, 1.73)	<0.001	95
Country				
US	1	1.26 (1.06, 1.50)	NA	NA
UK	2	1.94 (1.35, 2.78)	<0.001	94
European countries*	1	1.14 (1.03, 1.27)	NA	NA
Sample size				
<100 000	3	1.50 (0.98, 2.29)	<0.001	96
≥100 000	1	1.63 (1.55, 1.71)	NA	NA
Follow-up years				
<10	2	1.45 (1.13, 1.87)	0.005	87
≥10	2	1.63 (0.80, 3.32)	<0.001	98
Multimorbidity measurement				
Self-report	3	1.33 (1.03, 1.73)	<0.001	95
Examination/Health records	1	2.36 (1.97, 2.81)	NA	NA
Disease range#				
<20	3	1.50 (0.98, 2.29)	<0.001	96
≥20	1	1.63 (1.55, 1.71)	NA	NA
Dementia measurement				
Self-report	2	1.17 (1.07, 1.28)	0.34	0
Health records	2	1.94 (1.35, 2.78)	<0.001	94
Sensitivity analysis				
Leave-one-out				
-Ben Hassen 2022	3	1.33 (1.03, 1.73)	<0.001	95
-Calvin 2022	3	1.50 (0.98, 2.29)	<0.001	96
-Chen 2022	3	1.62 (1.19, 2.22)	<0.001	96
-Veronese 2023	3	1.69 (1.29, 2.21)	<0.001	92

HR, hazard ratio; CI, confidence interval.
* : Excluding UK.
# : Numbers of chronic diseases used to construct multimorbidity.

Table 5
Egger's test for publication bias.

Exposure	Study (n)	Egger's test	
		t value	p value
Multimorbidity and dementia			
Multimorbidity	4	2.09	0.172
CMM and dementia			
Diabetes	3	5.88	0.107
Heart diseases	3	1.25	0.430
Stroke	3	3.30	0.187
Diabetes + heart diseases	3	1.75	0.330
Heart diseases + stroke	3	1.89	0.309
Diabetes + stroke	3	4.92	0.128
Diabetes + heart diseases + stroke	3	1.29	0.419

CMM, cardiometabolic multimorbidity.

impacts of number of diseases, multimorbidity clusters, and multimorbidity trajectory on risk of dementia were narratively summarised due to lacking comparable studies. AD and VaD were also identified as secondary outcomes, but their associations with multimorbidity were inconclusive. The positive association between physical and psychological multimorbidity and risk of dementia was reported only in one study and therefore was narratively described in our review. This study provides valuable insights into the research priorities in multimorbidity and dementia, both of which challenge public health globally, and suggest that tackling multimorbidity will also reduce burdens of dementia on societies and healthcare systems.

Chronic diseases and dementia may share common aetiologies, involving genetic, environmental, lifestyle-related factors. Many diseases and dementia are partially heritable, and some CMD-relevant genes (e.g., Apolipoprotein E, fat mass and obesity-associated protein, insulin degrading enzymes, and the angiotensin-converting enzyme) have been found to influence dementia risk [36–41]. Genetic susceptibility to coronary artery disease has also been found to modify dementia risk after cardiovascular disease, perhaps through shared risk factors [42]. Socioeconomic deprivation, and lack of social support and other environmental factors play a distinctive role in the development of chronic diseases and dementia [29,43,44]. A large body of literature regarded lifestyles, including obesity, physical inactivity, diet, and alcohol consumption, as well-established risk factors common to both chronic diseases and dementia [29,45,46]. Although other systematic reviews have suggested that many long-term diseases were predictive of dementia onset, such as hypertension, diabetes, stroke and psychological disorders, no synthesised evidence on the association between multimorbidity and risk of dementia existed [9–12].

It is likely that multimorbidity may have cumulative effects of chronic diseases and eventually lead to onset of dementia [47]. This systematic review showed that multimorbidity, defined as the coexistence of two or more chronic diseases, was associated with higher risk of dementia, despite of high heterogeneity. In addition, chronic diseases are likely to cluster in the same person following specific patterns, therefore we identified two specific multimorbidity patterns, CMM and physical and psychological multimorbidity. The dose-dependent association between the number of CMDs and dementia, as well as the relationship between different CMM combinations and dementia supports the cumulative and specific effects of chronic diseases, while the effects of physical and psychological multimorbidity need more verifications.

Two pathological processes, the cerebrovascular and neurodegenerative pathologies, support the positive link between multimorbidity and dementia. Cardiovascular diseases will lead to reduced cardiac output and chronic cerebral hypoperfusion, thereby altering cerebral blood flow velocity and contributing to the development of vascular brain lesions [48]. Cerebral hypoperfusion also triggers brain hypoxia and im-

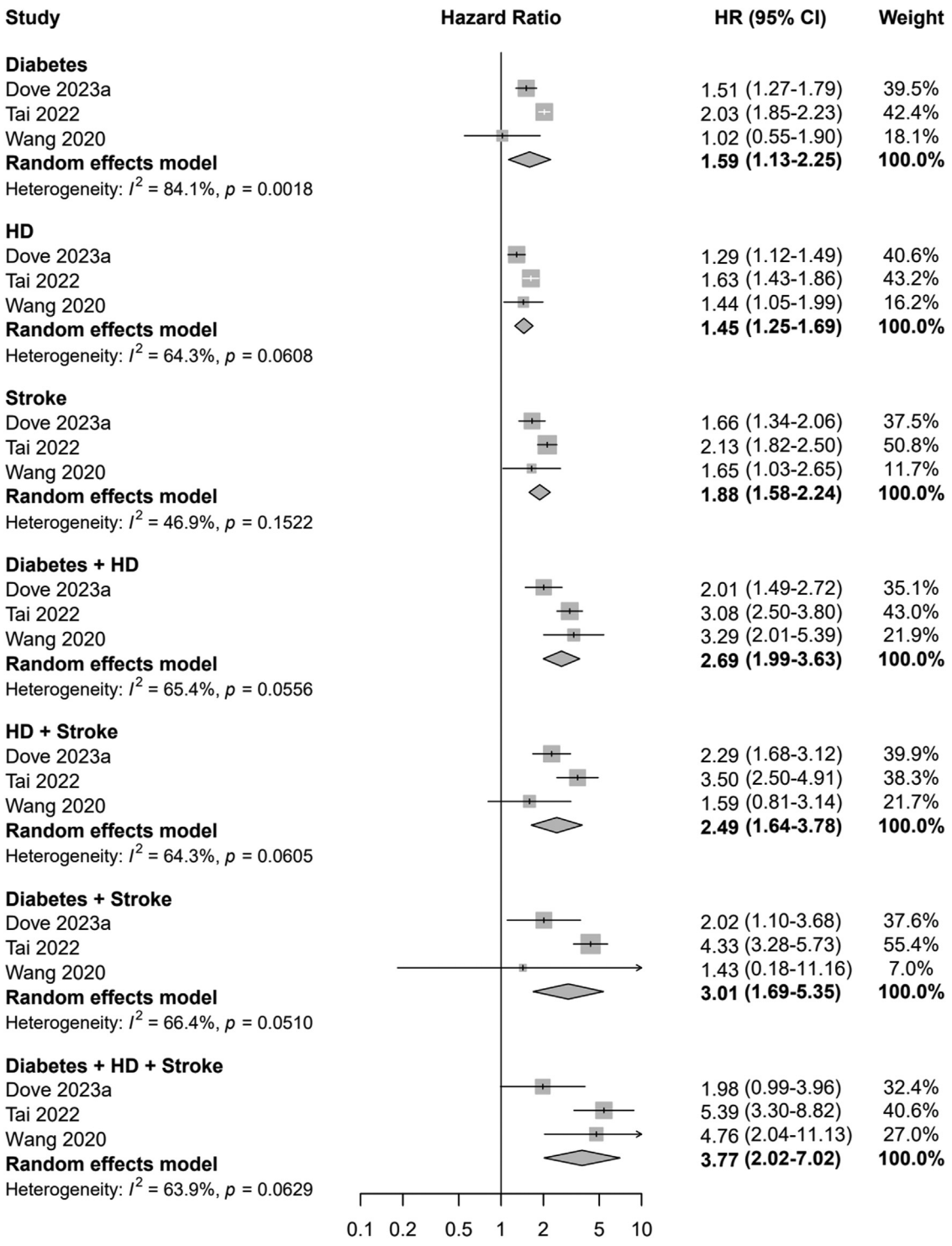

Fig. 3. Meta-analysis of the impact of the combinations of cardiometabolic diseases and dementia.
HR, hazard ratio; CI, confidence interval; HD, heart diseases.

pairs peptide clearance, promoting the deposition of amyloid-β [49]. In addition, the endothelial dysfunction caused by cardiovascular diseases can disrupt the integrity of the blood–brain barrier, leading to impaired amyloid-β clearance [50]. On the other hand, the chronic cerebral hypoperfusion and the disruption of blood-brain barrier lead to neurological insults, including brain infarcts and an increased load of white matter lesions [51]. Cerebral insulin resistance, characterising diabetes, has been linked to tau hyperphosphorylation and increased generation of amyloid-β [52]. Oxidative stress induced by chronic diseases (e.g., hypertension, diabetes) will cause cerebral atherosclerosis as well as neurodegeneration [52]. Although we did not pooled the risk of AD and VaD in meta-analysis, a more pronounced risk of VaD than that of AD was found in all primary studies, indicating that both neurodegenerative and vascular pathologies may be involved. Furthermore, multimorbidity may reflect an age-related multisystem failure, which is also an important character of cognitive decline and dementia [53,54]. Older adults with high inflammatory markers have a higher number of chronic diseases, and the low-grade chronic proinflammatory state may

ultimately the brain function [55–57]. The underlying mechanisms for the association between psychological disorders and dementia were unclear, with previous research interpreting the former as a risk factor or a prodromal manifestation of dementia. Specifically, depression is related to an imbalance in stress hormones, changes in brain structure, and increased systemic inflammation, which further impairing cognitive function [58,59]. From the psychosocial perspective, individuals with musculoskeletal disorders (e.g., osteoporosis) or painful diseases are limited to physical activity and social engagement, which also increases risk of dementia [23]. In addition to the individual pathways from chronic diseases, the accumulation of chronic diseases increases the possibility of polypharmacy and the complexity of treatment, thereby affecting brain and causing neural injuries [60].

In this systematic review and meta-analysis, meta-regression analysis was conducted to investigate potential sources of heterogeneity and modifiers, but no variables were observed to be significant modifiers. However, using self-report to measure dementia presented smaller magnitude for the association between these two conditions with no between-study heterogeneity, perhaps due to recall bias and social disability bias, leading to underestimation of chronic diseases and dementia [61–63]. Future research using available health records will be able to minimize the risk of misclassification and to better reflect multimorbidity as an early warning sign for dementia or other neurodegenerative diseases.

4.1. Clinical and public health implications

This present systematic review provides evidence on the predictive ability of multimorbidity for risk of dementia, having important implications in terms of prevention and clinical practice. First, as existing recommendations typically focus on chronic diseases individually, guidelines and recommendations taking account of multiple chronic diseases should be adapted to reduce the possibility of polypharmacy and heavy treatment burden and therefore prevent downstream health deterioration. Second, an early holistic assessment of risk factors would promote the prevention of development of multimorbidity in middle-aged and older individuals—particularly those who already have chronic diseases—in order to maintain cognitive health. Third, clinicians and researchers should raise awareness of the associations of multimorbidity and multimorbidity patterns with dementia and incorporate multimorbidity when assessing the progression of dementia and deterioration of health. Furthermore, the close monitoring of individuals affected by multimorbidity is helpful to identify high-risk individuals of dementia, and therefore tailor clinical interventions aimed at dementia prevention. Fourth, risk factor modification appears critical for diminishing risk of dementia in patients with chronic diseases and multimorbidity. By health education promotion, social networking and support, lifestyle and leisure activities programs and so on, a cognitive reserve can be constituted to prevent the onset of dementia and other neurodegenerative diseases [64]. Finally, due to the long-term complex interplay between multimorbidity and dementia, organizational reform for the healthcare system is needed to shift the focus of care from "specialism" to "generalism" [65]. Strategies to achieve an integrated healthcare system may include community multidisciplinary teams, joint medical/psychiatry inpatient units, and care home intervention teams [66].

4.2. Strengths and limitations

Our study has several strengths. First, a thorough literature search was conducted in various databases as well as the reference lists of the eligible studies and relevant reviews, increasing our confidence that all relevant studies were included. Second, the restriction of cohort study design and the moderate to high quality of all included studies allows us to synthesise reliable evidence on the longitudinal effect of multimorbidity on risk of dementia. Third, we further identified two common multimorbidity patterns, CMM and physical and psychological multimorbidity to add more evidence on the clustering effect of multimorbidity. However, the following limitations must be considered. First, we only included studies published in English to avoid language misinterpretation, which might have excluded relevant cohort studies of multimorbidity and dementia in other language. Second, the included studies had different sample characteristics, follow-up time, multimorbidity and dementia measurement and were adjusted for different covariates, all of which might potentially contribute to the high heterogeneity observed in the meta-analysis. Although many common diseases like hypertension, diabetes and heart diseases were considered in most studies, determining the disease range and definition of multimorbidity can still be a priority [6]. In addition, several included studies used self-reported information of multimorbidity and dementia, which was subject to recall bias and social desirability bias. Third, although two common multimorbidity patterns were identified, only one study examined the effects of physical and psychological multimorbidity on dementia. More studies focusing on important multimorbidity patterns with high quality are warranted to estimate the risk of dementia. Fourth, the prevalence of both multimorbidity and dementia increased by age, but the role of age on the association between these conditions was unconclusive due to the limited information from primary studies. Finally, because the longitudinal association between multimorbidity and dementia was investigated only in recently years, current evidence has been almost exclusively in high income countries (especially in UK), therefore our findings may not be generalisable to other regions. Future longitudinal studies across varied cultures and settings are warranted to examine whether the association between multimorbidity and dementia can be replicated in middle-income and low-income countries.

5. Conclusion

There is convincing evidence showing a positive association between multimorbidity and dementia in middle-aged and older adults. Specific CMM combinations were also significantly associated with risk of dementia, while the effect of physical and psychological multimorbidity remain inconclusive. Although future longitudinal studies with different settings are needed, our findings underscore a holistic and integrated perspective to focus on both multimorbidity and dementia, and individuals affected by multimorbidity should be prioritised in risk factor modification and dementia prevention. Preventing the development of multimorbidity is also crucial—particularly those who already have one chronic disease—in order to maintain cognitive health.

Declaration of generative AI and AI-assisted technologies in the writing process

We have not used any AI at all.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yaguan Zhou: Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Yating You:**

Validation, Methodology, Data curation. **Yuting Zhang:** Validation, Data curation. **Yue Zhang:** Writing – review & editing, Validation. **Changzheng Yuan:** Writing – review & editing. **Xiaolin Xu:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

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Supplementary materials

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