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Review

A systematic review of targeted dementia risk reduction interventions in middle-aged adults in Primary Care

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A B S T R A C T

Background: Pathological changes of dementia are thought to commence in mid-life, making mid-life an attractive target for dementia risk reduction. This review assessed the current literature on multidomain dementia risk-reduction interventions in mid-life.
Methods: We systematically searched MEDLINE, CINAHL and EMBASE for eligible studies. Studies were included if (i) participants had a mean age between 45 and 65 years, (ii) the intervention was delivered in a primary care setting and targeted two or more dementia risk factors, and (iii) outcomes were change in cognitive function or change in risk score. Data was extracted and assessed for bias using the revised Cochrane risk-of-bias assessment tool.
Results: Seven studies were included. Participants' mean age ranged from 45.3 to 64.2 years. Interventions ranged from 10 weeks to 9.8 years and targeted between two and six dementia risk factors. There was a large variation in the type of outcome and statistical tests utilised across the included studies, impacting the ability to draw comparisons between the studies and draw conclusions regarding treatment effects. There was a high risk of bias in three of the studies and some concerns of bias in the other four studies. Two studies assessing dementia risk found a reduction in risk scores at their primary endpoint. None of the included studies found a statistically significant change in cognition from their interventions. This may be attributable in part to not assessing cognition prior to the interventions, limited risk factors being addressed, and the short follow-up/duration of the studies.
Conclusion: Current evidence for multidomain dementia risk-reduction interventions in mid-life is not definitive; however, given their substantive potential benefits and likely limited harms, they may be considered for implementation in clinical practice after further evaluation. Future trials that have longer follow-ups, target a broader range of dementia risk factors, and that use consistent outcome measures will be valuable. Strategies to maximise implementation of multidomain interventions and long-term effectiveness will enhance the evidence base for dementia prevention in primary care.

1. Background

Dementia is a major cause of disability and dependency among older adults worldwide, impacting more than 55 million people globally, projected to rise to 153 million by 2050 [1,2]. Studies suggest that dementia, especially Alzheimer's disease, could be a clinically silent disorder starting in mid-life, with symptoms only developing in later in life [2–4]. Given the lack of efficacy of current pharmacological therapies and expanding awareness that brain pathology may develop over many years or even decades, non-pharmacological approaches to dementia prevention in mid-life are critical. The best defence against dementia is still risk reduction [5,6], and there is increasing interest in identifying effective strategies for dementia prevention [5]. It has been estimated that up to 45 % of the cases of dementia cases worldwide are attributable to vascular risk factors and physical and cognitive inactivity [2].

Recognising the complex nature of cognitive decline and dementia, a 2021 Cochrane review highlighted the need to identify risk profiles in which there is an opportunity for targeted preventive interventions at the right point in time [7]. An intervention implemented too late may have missed the window for prevention [7]. However, an intervention implemented too early could prolong burden and challenges to adherence unnecessarily [7].

Evidence from large multidomain intervention trials such as FINGER [8] and HATICE [9] suggests preventive efforts may be more effective when targeting middle-aged people with multiple risk factors for dementia.

Primary care is recognised to be the setting for preventive interventions [10], and the principal target for initiatives to promote preventive care [11]. The United States Preventive Services Task Force (USPSTF) specifically recommends primary care interventions to reduce risk factors for cognitive impairment, including tobacco cessation, reducing alcohol use, healthful diet, physical activity, falls prevention and screening for high cholesterol, hypertension, and depression [12]. These recommendations are explicit for preventive activities within primary care, rather than wider-level public health preventive activities that primary care clinicians might contribute to [12,13]. Primary healthcare has a role in determinants of health, health promotion and disease prevention, and primary health and community health [14]. It is well-equipped

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to provide scalable multidomain preventive interventions to patients in their midlife (45–65 years), systematic reviews have demonstrated that preventive interventions in the primary care setting can be effective in changing patient behaviour for modifiable risk factors associated with dementia, including alcohol consumption, increasing physical activity, smoking cessation and weight loss. The modifiable risk factors for dementia are also linked with several other chronic health conditions and outcomes; managing them can help prevent premature mortality and promote healthy aging [15–17].

Primary care is increasingly person-centred (as opposed to disease-centred), providing an access point to the broader health system and enabling continuity and coordination of care over a person's lifetime [14,18]. Visiting a community-based primary care service at least once per year is associated with an increased rate of patient compliance with evidence-based guidelines for preventive health interventions, which in turn improves health outcomes [18]. Integrating dementia prevention interventions with acute care or other preventive interventions in this setting holds potential for public health benefits. Previous studies have examined the barriers and enablers to working with patients to reduce dementia risk and found the most frequent reported barriers were patients' lack of motivation to hear about dementia prevention and the limitations of the current work structure in primary care [19]. Studies on achieving change in primary care have shown that the challenges associated with implementing any type of change in primary care is complex; ensuring the intervention "fits" the context of primary care is essential for success [20].

Several studies and reviews on multidomain interventions to prevent dementia have been conducted [7]. However, to date, none have focused explicitly on trials conducted in primary care that utilised multidomain interventions to reduce dementia risk or improve cognition in individuals aged 45–65. Multidomain dementia risk reduction interventions in primary care, especially focusing on middle-aged adults, are gaining momentum [21]. We aimed to systematically review the effectiveness of multidomain interventions in primary care for improving cognition or reducing dementia risk in middle-aged adults.

2. Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. The protocol for the review was not prospectively registered, but a protocol was developed a priori and followed throughout.

2.1. Search methods for identification of studies

A clinical librarian assisted in identifying appropriate search terms for the review. Titles and abstracts of articles in three databases (Ovid MEDLINE, EMBASE and CINAHL) from 1947 until 18th September 2023 were searched using Medical Subject Headings (MeSH) terms and keywords. The search strategies for each database are available in the appendix. The search was limited to only articles examining individuals in midlife (45–65 years). The data were uploaded and screened through Covidence [23] by a team of four reviewers. At least two reviewers independently reviewed each abstract against the inclusion criteria. The full texts of potentially eligible studies were then obtained and further scrutinised. A third reviewer (arbitrator) resolved any disagreements between the two reviewers. Reference lists of individual studies were manually screened for additional relevant publications.

3. Inclusion criteria

3.1. Types of studies

We included before-and-after studies, randomised controlled trials (RCTs), and controlled and uncontrolled interventional studies. We excluded pilot studies and protocol papers but conducted a forward citation search to determine if full trial results were available in a separate publication. Only studies published in English were included due to limited resources to provide reliable translations. If more than one publication used data from the same study, the most recent or complete publication was selected.

3.2. Types of participants

Studies were eligible if the mean age of included participants was between 45 and 65 years (mid-life), and they utilised a community-based sample in a primary care setting. For this review, we defined primary care as any community-based healthcare setting providing whole-person care for health needs throughout the lifespan; the person delivering the intervention did not need to be a primary care provider or have specific qualifications [24,25]. We excluded studies in which participants had a current diagnosis of dementia or mild cognitive impairment.

3.3. Types of interventions

In line with previous systematic reviews on multidomain interventions for dementia prevention [7], we included studies using interventions targeting ≥2 of the potential risk factors for dementia identified by the Lancet Commission that could be addressed in a primary care setting: cognitive inactivity, hearing loss, high low-density lipoprotein (LDL) cholesterol, depression, physical inactivity, diabetes, tobacco smoking, nutritional modifications, hypertension, obesity, excessive alcohol consumption, social isolation, and visual loss [2].

To date single domain prevention trials have only shown limited efficacy for specific interventions [24]. Multidomain interventions may be more effective than those targeting single risk factors due to the multifactorial causes of dementia, and from additive or synergistic interactions between the different risk factors [26–28].

3.4. Types of outcomes

We included studies that reported cognition or dementia risk as a primary or secondary outcome. Eligible cognitive outcomes had to be measured objectively by standardised neuropsychological tests, including tests of global cognition, tests of an individual cognitive domain, or composite scores combining scores from a battery of different tests. Eligible dementia risk outcomes were one of three validated dementia risk scores: Cardiovascular risk factors, Aging and Incidence of Dementia (CAIDE) [29], Lifestyle for Brain Health Index (LIBRA) [30], and the Australian National University Alzheimer Disease Risk Index (ANU-ADRI) [31].

3.5. Data extraction

Using a standardised form, two reviewers independently extracted the following information: author, year, country, study population, intervention and control conditions, attrition, outcome type, outcome measures, outcome value, effect direction, and effect significance.

Two reviewers independently assessed the risk of bias in the studies using the Cochrane risk-of-bias assessment tools (RoB2) [32]. The risk of bias was categorised as "low" (no concerns in any domain), "some concerns" (concerns in 1+ domains), or "high" (high risk of bias in 1+ domains).

Outcome measures were classified into two types: change in cognitive function or change in risk score. Based on eligibility criteria reported within each trial, we categorised study populations into two types:

1. At risk, i.e. all participants were considered to be at an increased risk of developing dementia (compared to the general population), based on genetic, biological, imaging, clinical, family history and/or lifestyle risk factors; and,

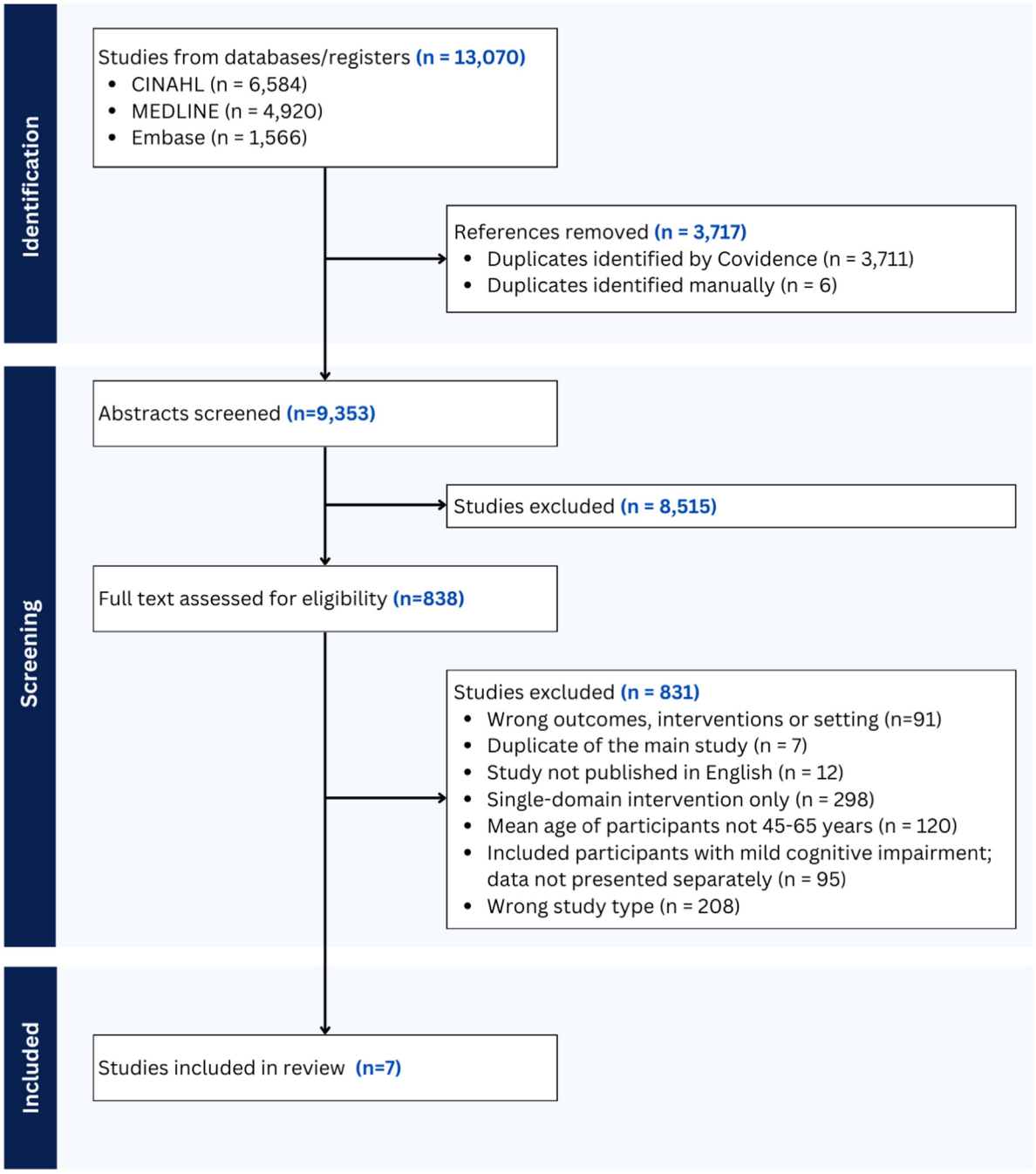

Fig. 1. Flow diagram.

2. The general population, i.e., study participants were not selected based on any specified risk factors other than age.

3.6. Data synthesis

Studies were grouped based on outcome measure, (either cognition or dementia risk score) and significance of result.

Due to the heterogeneity of the interventions a meta-analysis was not possible, so a narrative synthesis only was used to analyse the results.

4. Results

4.1. Study selection

The flow diagram for the review is shown in Fig. 1. The systematic search resulted in 13070 articles, of which 3717 total duplicates were removed (Fig.1). A total of 838 full text studies were assessed, of which 831 were excluded. Seven studies were included in the final review. The references for these studies can be found in Appendix 2.

4.2. Study characteristics

Table 1 summarises data extracted from the included studies. Seven studies involving 5189 participants were published between 2008 and 2023. These studies were conducted in Australia ($n = 2$), Finland ($n = 1$), Hong Kong ($n = 1$), The Netherlands ($n = 1$), and the USA ($n = 2$). Mean age of participants ranged from 45.3 to 64.2 years. The duration of interventions ranged from 10 weeks to 9.8 years. All included studies used a randomised controlled design.

The only study that recruited participants without risk factors (general population) was Yu 2021 [33]; all other studies identified individ-

Table 1
Summary of included studies.

Trial Name (If given), Lead Author, Location & Publication Year	Sample Size (N)	Setting	Duration	Target population	Mean Age (SD)	People delivering Intervention
1. Body, Brain, Life (BBL) Anstey, 2015, Australia	176	Internet based vs face to face in general practice	3 months	Individuals with risk factors	Control: 55.5 (2.9) BBL + FF: 55.4 (3.1) BBL: 55.6 (2.9)	One group internet only, 2nd group had face to face sessions with a clinical psychologist.
2. BBL-GP, Anstey, 2020, Australia	125	Hybrid of general practice (face to face) and online	12 week intervention with follow-up to 62 weeks.	Individuals with risk factors	BBL-GP: 51.14 (14.24) LMP: 51.41 (11.69) Control: 49.95	Allied health (Nutritionist and exercise instructor)
3. Look AHEAD, Hayden, 2021, US	3938	Study Centre (usual medical care was still delivered by their regular medical practitioner)	9.8 years (intensive intervention for 4 years)	Individuals with risk factors	58.85 (6.86)	Lifestyle counsellor
4. ADDITION, Koekkoek, 2012, Netherlands	183	General Practice	6 Years	Individuals with risk factors	Intensive treatment: 59.3 (5.6) Routine Care: 59.5 (5.3)	General Practitioners
5. Diabetes Prevention Study, Luchsinger 2017 & Luchsinger 2015, Finland	364	Specially designed study centre employing a physician, study nurse and nutritionist. An exercise instruction / physiotherapist was also a member of the study team.	4 years (cognition assessed 9 years after the intervention)	Individuals with risk factors	63.1 (10.7)	Multidisciplinary team (Nutritionist regularly + study physician annually).
6. Masley 2008, United States	56	Wellness Centre*	10 weeks	Individuals with risk factors (individuals exercising less than 3 days per week)	Entire cohort: 45.3 years Intervention group: 47.1 Control group: 43.5	Allied Health (Nutritionist and exercise instructor)
7. Yu 2021, Hong Kong	347	Elderly centres**	12 weeks	General population	64.2 (6.4)	Interventional Researchers

uals with various dementia risk factors, including sedentary behaviour, high body mass index, and type 2 diabetes. The breakdown of the risk factors examined in individual studies is presented in Table 3. In all studies except Yu 2021 [33], the intervention was delivered by multidisciplinary teams comprising general practitioners, clinical psychologists, lifestyle counsellors, nutritionists, and exercise instructors. In Yu 2021 [33], the intervention was delivered by research staff.

4.3. Risk factors targeted

Of the 13 risk factors of interest, [2,27] the included studies addressed 2–6 risk factors (Table 2). None of the studies addressed hazardous alcohol drinking, high LDL cholesterol, visual loss, or hearing loss. Hypertension and depression were addressed in one study each.

4.4. Risk of bias

The risk of bias in the included studies is presented in Table 3. The overall risk of bias was judged to be high in three studies and had some concerns in four studies. Bias was mainly related to inadequate reporting of outcome data.

4.5. Measures of treatment effect

Of the seven included studies, only one study reported a significant effect of the intervention relative to a control group [34]. Four studies reported a significant effect of the intervention relative to baseline [34–37].

There was a large variation in the types of outcomes and analyses performed across the included studies. Two studies reported ANU-ADRI as the primary outcome [38,39]; the other five studies evaluated cognition using composite scores [33–37,40]. Reported outcome measures and intervention effects are summarised in Table 4. Given the heterogeneity of reported findings, we were unable to comment on the magnitude of effects or the impacts of different sample sizes.

Of the two studies with dementia risk reduction as the primary outcome, only the second study demonstrated a significant decrease in ANU-ADRI scores in the intervention condition relative to the control [38,39]. The first Body Brain Life (BBL) study utilised an online-only and a face-to-face augmented multidomain intervention to reduce dementia risk. Both groups demonstrated significant reductions in ANU-ADRI score at 26 weeks; the online group had a reduction of 2.36 points, and the face-to-face group had a reduction of 1.56 points. The study had limitations, mainly inadequate power to detect significant differences between the online and face-to-face groups and the short duration of the trial (26 weeks) [38].

The second Body Brain Life (BBL) study was the most promising study included in this review, utilising holistic interventions targeting physical inactivity, diet, obesity, social inactivity and [39]. It demonstrated that a multidomain primary care intervention was effective in reducing the risk of dementia for a period of at least 15 months [39]. The study was also most aligned with the primary care environment with the selection of patients comparable to general practitioners' usual care of identifying patients with risk factors for chronic disease [39]. The intervention utilised specialist practitioners to deliver the physical activity and nutrition sessions tailored to the individual client's clinical profile [39]. The control arm (generic healthy lifestyle management program that was not personalised) did not result in dementia risk reduction relative to baseline [39]. The study had several limitations including being underpowered, having a high attrition rate and its relatively short length of follow-up [39].

Of the five studies that evaluated cognition using composite scores, none found a statistically significant change in cognition. There were two short-duration studies; Masley 2008 (10-week intervention) [40], and Yu 2021 (3-month intervention) [33]. Both these studies found improvement on several individual cognitive tests but no statistically significant difference in the composite score. Hayden 2021, Koekkoek

Table 2
Risk factors addressed in included studies.

Risk factor (% of dementia cases attributed)	Physical Inactivity (2%)	Tobacco smoking (2%)	Diet[a]	Hazardous alcohol drinking (1%)	Cognitive inactivity	Obesity (1%)	Hypertension (2%)	Social inactivity (4%)	Diabetes mellitus (2%)	High LDL Cholesterol (7%)	Depression (3%)	Visual loss (2%)	Hearing loss (7%)	Count of risk factors targeted
1. Anstey 2015														4
2. Anstey 2020														5
3. Hayden 2021														4
4. Koekkoek 2012														5
5. Luchsinger 2015														4
6. Masley 2008														2
7. Yu 2021														2

[a] Nutritional epidemiology studies often but inconsistently report an association between diet and biomarkers, cognitive decline, dementia or Alzheimer's disease. Eating a diet high in fruit and vegetables and low in ultra-processed foods is beneficial for many health conditions. It affects the dementia risk factors of obesity, diabetes and hypertension, but insufficient evidence exists to say that this diet is directly helpful for dementia prevention [2].
Red= not addressed, Green= part of intervention, Yellow= only education provided.

Table 3
Risk of bias in included studies.

Included study	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
1. Anstey 2015	Low risk	Low risk	Some concerns	Some concerns	Low risk	Some concerns
2. Anstey 2020	Low risk	Low risk	Some concerns	Some concerns	Low risk	Some concerns
3. Hayden 2021	Some concerns	Low risk	Some concerns	Low risk	Some concerns	High risk
4. Koekkoek 2012	Some concerns	Low risk	Some concerns	Some concerns	Some concerns	High risk
5. Luchsinger 2015	Low risk	Low risk	Some concerns	Low risk	Some concerns	Some concerns
6. Masley 2008	Low risk	Low risk	Some concerns	Some concerns	Some concerns	High risk
7. Yu 2021	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns

2012 and Luchsinger 2015 showed no difference in mean cognitive score compared to their control groups. These studies did not assess cognition prior to the intervention; cognition was first assessed three years post-intervention in Koekkoek 2012 [36], eight years post-intervention in Hayden 2021 [35] and nine years after the active intervention in the Luchsinger 2015 [34].

It should be noted that the effects of the Look AHEAD intervention on weight loss were most pronounced at 12 months post-randomisation and attenuated thereafter [35]. The ADDITION study and the Finnish diabetes study did not report if their primary outcomes were maintained post-intervention [36,34]. The efficacy of behavioural and lifestyle interventions may decrease over time and/or once the intensity of the intervention reduces.

5. Discussion

The systematic review of multidomain interventions in primary care for dementia prevention in middle-aged adults identified only seven studies. The reporting of the study outcomes was highly variable, with no consistent effect measure, making a meta-analysis inappropriate.

The Lancet Commission indicated in their 2024 report that risk reduction should target risk factors present throughout the lifespan (see Table 2) [2]. None of the included studies addressed the majority of the known risk factors. The exclusion of certain risk factors such as hazardous alcohol drinking, smoking and social isolation is a notable gap particularly with many of the excluded risk factors clustering around inequalities and being more common in vulnerable populations.

The Lancet Commission reported that if hearing loss (7 %), visual loss (2 %), high LDL cholesterol (7 %) and hazardous alcohol drinking (1 %) were eliminated, there would be a resultant 17 % reduction in dementia cases; however, none of the included studies addressed any of these risk factors. Three out of the seven included studies utilised multidisciplinary teams to deliver their interventions, as recommended by the Lancet Commission.

Given the long latency period for the presentation of dementia symptoms, assessing cognition over a short time period may not capture the cognitive benefits of multidomain interventions [2]. No consensus has been established about the optimum instruments to use to measure cognitive decline, and many cognitive tests have suffered from learning or practice effects. As research moves towards intervention earlier in the life course there is a need to develop more sensitive measures of cognitive function that are suitable for repeated use over time.

In the studies conducted over longer than 12 months and included in this review, no baseline cognitive assessments were done, hence it is impossible to know if there were statistical differences in the baseline cognitive function of the two groups and if cognition had changed since baseline. This finding poses a problem for interpretation of the data as meaningful results should be based on a specific and prespecified analysis plan and none of the studies on cognition that had a duration of longer then 12 months had assessment of cognition in the main study protocol. The primary outcomes targeted attenuated in one study after the intervention ceased, and the long term impact on dementia risk were not reported in the other two studies [33,35–37]. The long-term maintenance of health behaviours associated with reduced dementia

Table 4
Outcome Measures and Intervention Effects.

Study	Intervention	Comparison / Control	Outcome Measured	Difference in Outcomes	p value
1. Anstey 2015	Education: General dementia literacy and familiarization with risk and protective factors. Specific education on: physical activity, diet, social engagement, cognitive engagement and management of chronic conditions. Face to face group also received group sessions based on risk factors delivered by a clinical psychologist.	Emailed health related advice	Change in ##ANU-ADRI	BBL- FF* (at 12 weeks): $Z = -0.25$ BBL (at 12 weeks): $Z = -0.25$	$p = 0.021$ $p = 0.008$
2. Anstey 2020	The Body, Brain, Life-GP intervention was a 12-week program that included the above learning modules tailored, face-to-face physical activity and nutrition sessions	Emailed health related advice	Change in ##ANU-ADRI	BBL-GP vs control (at week 62): −3.06 LMP** vs control (at week 62): −1.24	$p = 0.1$ $p = 0.5$
3. Hayden 2021	Diet: Participants had a daily calorie goal of 1200 to 1800 kcal/day based on initial weight. The diet specified <30 % total calories from fat (<10 % saturated fat) and a minimum of 15 % total calories from protein. Physical activity: Similar in intensity to brisk walking for at least 175 min/week. Obesity management: Goal of at least 7 % weight loss at one year and maintenance over the course of the study.	Diabetes support and education	Cognition composite: modified mini mental status exam, digit symbol coding, ###RAVLT Immediate, RAVLT Delayed, Stroop, Trails A and B	####CVD History: ^LSMEAN = 0.01 No CVD History: LSMEAN = −0.07	$p = 0.253$
4. Koekkoek 2012	Intensive multifactorial treatment consisted of lifestyle advice regarding diet, physical activity and smoking and promotion of protocol-driven strict regulation of metabolic parameters.	Routine Care	Cognition: (composite score; including the domains memory, information-processing speed and attention and executive function)	Mean difference in composite Z-score at first assessment (3 years post intervention): z-score 0.00; 95 %-CI −0.16 to 0.16	No difference
5. Luchsinger 2015	The intervention group received individualized dietary, exercise, and weight reduction counselling.	Usual care	Cognition Finnish CEARD battery: CVLT*****, digit symbol coding, D-KEFS# letter, D-KEFS category)	Mean score control group: 82.3 Mean score intervention group: 81.6	$p = 0.49$
6. Masley 2008	Taught via weekly lectures about meal plans and recipes for a diet with >30 g of fibre and <16 g of saturated fat daily. There were encouraged to reach 70 % to 85 % of their maximum achieved heart rate 5–6 days per week for 30 min and to perform strength training 3 days per week for a total of 10 weeks.	Control group	Cognition: (mental speed, reaction time & cognitive flexibility)	Mental speed % improvement 4.6 % Reaction time % Improvement 4.50 % Cognitive flexibility % Improvement 11.60 %	$p = 0.019$ $p = 0.18$ $p = 0.019$
7. Yu 2021	A 12-week computerized cognitive training (CCT) intervention using touch-screen video game technology preceded by physical activity and an active control among community-dwelling older adults.	Video watching and physical activity	Cognition (Change in rapid cognitive screen)	Multidomain computerised cognitive training (CCT) and physical activity 0.6 (SD 2.0) Two-Domain CCT + PE 0.5 (SD 1.8)	$p = 0.002$ $p = 0.004$

*Body Brain Life Face to face. **Body Brain Life General Practice. ***Lifestyle modification program. *****California Verbal Learning Test. #Delis-Kaplan Executive Function System. ##Australian National University Alzheimer's Disease Risk Index. ###Rey Auditory Verbal Learning Test. ####Cardiovascular disease. ^least squares means.

risk was unclear; it is unknown if the cognitive benefits dissipated as the other benefits from the intervention dissipated. These studies did not demonstrate a reduction in obesity and the linked condition of diabetes across the life course, as recommended by the Lancet Commission [4].

Population-based research has shown that participants aged 60–64 years with a one-point lower ANU-ADRI at baseline had an 8 % lower chance of developing mild cognitive impairment or dementia over a 12-year period [40]. The Body Brain Life studies demonstrated an opportunity for dementia prevention programs to be implemented in primary care. However, the evidence is not yet robust enough that multidomain interventions in primary care for middle-aged adults can be recommended for widespread implementation.

To be feasible in primary care preventive interventions must be inexpensive and easy to implement. To be acceptable to consumber and healthcare professionals, preventive interventions must also fit with the current structure of primary care and build on the existing structures [20].

This review was conducted following the Cochrane guidance to ensure the methodology was robust and systematic. The articles were screened independently by a team of four reviewers reducing bias in the study selection phase. The reporting of the search strategy followed the requirements of the PRISMA statement. Opportunities for pooling data for meta-analysis were explored but limited due to the heterogeneity in the reporting of the outcomes of the interventions, and conclusions were therefore based on narrative synthesis. This study may have been affected by language bias due to it being restricted to articles only published in English; there are ethnic/cultural differences in attitudes to dementia, including definitional differences. It is possible that non-English publications may have been affected by their culturally based understandings of and attitudes to dementia [41]. Thus, it is possible that inclusion of non-English literature could have further increased the

heterogeneity of the review findings.. All of the included trials had a risk of bias in at least two of the domains as per the Cochrane risk of bias tool.

There are public health risks in inaction on dementia prevention while awaiting the results of RCTs, and waiting for successful RCTs for implementing these strategies may be counterproductive. There is not yet robust evidence that multidomain interventions for dementia prevention in primary care are effective. Nevertheless, advice from the World Health Organization and clinical guidelines demonstrate that there is an unjustifiable risk to public health in waiting for a stronger evidence base [42]. Health professionals in primary care should continue to offer preventive interventions focused on dementia risk factors to patients in mid-life, given their potential benefits beyond dementia and limited harm from this approach.

Traditional RCTs are difficult to conduct in the area of dementia risk reduction. Large sample sizes and long follow-up periods are required and strict double-blinding may not be possible with lifestyle-related interventions.

The 2024 Lancet Commission recommended that future studies report the mean follow-up of people who develop and do not develop dementia separately and/or test the effect of excluding incident cases that develop within 5–10 years of follow-up. Large-scale holistic studies are needed that address all aspects of health, including social, cognitive, physical, and vascular health. These studies should address the need for long-term behaviour change to promote positive health behaviours in later life.

6. Conclusion

Current evidence for multidomain dementia risk-reduction interventions in mid-life is not definitive. This review highlights the paucity and substantial heterogeneity in dementia prevention trials in primary care, particularly in outcome measures. While the evidence is not yet definitive, interventions for dementia risk reduction in primary care are recommended by clinical guidelines, have substantive potential benefits, and are unlikely to cause harm. Therefore, they may be considered for implementation in clinical practice.

The trials showing beneficial results in some areas can be regarded as concept studies. Future research should seek to replicate these findings in larger trials with longer follow-up periods. Future trials should also take a holistic approach, targeting a broader range of dementia risk factors beyond diet and exercise. Future trials should account for the links between the risk factors for dementia and that simultaneous reductions in several factors could provide greater benefits. Consistency in outcome measures would enable comparison of effect sizes across different types of interventions. Strategies to maximise implementability (i.e. appropriateness, acceptability, feasibility, sustainability) and long-term effectiveness of dementia prevention interventions in primary care should be evaluated. Enhancing the evidence base for dementia risk reduction interventions in middle-aged adults in primary care could potentially reduce the future burden of dementia on governments, communities, families, and individuals.

Statement of conflict of interest

The first three authors disclose a potential conflict of interest regarding involvement with the HAPPI MIND clinical trial.

Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The first 3 authors on this manuscript are also working on a clinical trial on this topic (HAPPI MIND). If there are other authors, they 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

Mary Tullipan: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Johnson George:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Parker Magin:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Kali Godbee:** Writing – review & editing, Supervision, Software, Investigation, Formal analysis. **Jane Ferns:** Writing – review & editing, Validation, Formal analysis. **Claire Frewin:** Writing – review & editing, Validation, Formal analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100187.

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