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Exercise for Dementia Prevention: Evidence Supporting Flexible, Personalized Physical Activity Prescriptions

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Abstract

Background: Dementia is a leading cause of disability in older adults, and physical inactivity is a modifiable risk factor. It is unclear whether total weekly activity volume or its temporal distribution matters more for dementia risk, and how observational findings relate to trial evidence.

Aim: To critically appraise recent evidence on physical activity volume and pattern in relation to dementia risk, to summarize the level of evidence for proposed biological mechanisms, and to outline a consensus-based exercise prescription framework, keeping these three kinds of evidence distinct.

Methods: Narrative review prepared according to the Scale for the Assessment of Narrative Review Articles (SANRA). PubMed/MEDLINE was searched for English-language publications from January 2015 to August 2026 and supplemented by reference-list screening. Cohort studies, randomized trials, meta-analyses, and consensus statements were eligible. Evidence was synthesized narratively, without pooling or formal risk-of-bias grading.

Results: In a UK Biobank accelerometer cohort (n = 91,512), more than 300 minutes/week of moderate-to-vigorous physical activity (MVPA; ≥3 metabolic equivalents) was associated with lower dementia incidence than less than 300 minutes/week, whether concentrated in 1–2 days (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.60–0.89) or regularly distributed (HR 0.79, 95% CI 0.64–0.98); the two patterns did not differ significantly (HR 0.91, 95% CI 0.70–1.18). Two further weekend-warrior analyses used overlapping UK Biobank data, and one independent cohort with self-reported activity reported a concordant association with mild dementia. Among participants below the MVPA threshold, light physical activity above 840 minutes/week was associated with lower dementia incidence, but the effect estimate is not numerically available in the source. A meta-analysis of randomized trials found a smaller effect on global cognition (standardized mean difference 0.29, 95% CI 0.17–0.41).

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Limitations: The evidence is predominantly observational and dominated by one cohort, and is open to reverse causation, residual confounding, and healthy-volunteer bias. The review is narrative and based on a single database.

Conclusions: Higher physical activity volume, whether concentrated or distributed, is associated with lower dementia risk in observational data, but causality cannot be inferred and trial effects on cognition are smaller. Supervised multicomponent exercise consistent with international consensus guidance is a reasonable, low-risk recommendation for older adults; its role in dementia prevention remains to be confirmed.

Keywords: Dementia prevention; physical activity; exercise prescription; cognitive aging; healthy longevity; personalized medicine.

1. Introduction

Dementia is among the leading causes of disability and dependency in older adults worldwide. More than 57 million people were living with dementia globally in 2021, and the World Health Organization projects approximately 78 million cases by 2030 and 139 million by 2050 as populations age [1]. These projections carry substantial uncertainty, because they depend on future trends in life expectancy, risk-factor exposure, and diagnostic capacity, and other modelling approaches, such as the Global Burden of Disease forecasts, have produced different estimates [2].

Currently available pharmacological treatments provide at most modest clinical benefit and have not been shown to prevent dementia at the population level. This has focused attention on modifiable risk factors. The 2024 report of the Lancet standing Commission identified 14 modifiable risk factors across the life course, including physical inactivity, which together account for an estimated 45% of dementia cases through their population-attributable fraction [3]. This estimate assumes causal relationships and combines risk factors; it does not imply that any single factor, physical activity included, can eliminate risk in isolation.

Within this framework, physical activity is a candidate prevention target, but the dose and pattern of activity required are uncertain. Guidelines have traditionally emphasized frequent, evenly distributed activity of moderate-to-vigorous intensity (MVPA, ≥3.0 metabolic equivalents [METs]; light physical activity [LPA] is approximately 1.6–2.9 METs). Several accelerometer-based cohort studies published since 2024 have asked whether concentrating the recommended volume into one or two days per week (a “weekend warrior” pattern) is associated with comparable dementia risk [4–6]. The question is relevant to older adults facing occupational, caregiving, mobility, or health-related barriers to daily exercise. The minute-based thresholds discussed in this review derive from accelerometry in the cohort studies and are interpretable only with reference to the measurement method (Section 2.5). The weekend warrior pattern has been studied more extensively for mortality and cardiovascular outcomes [7–9].

A second uncertainty concerns the gap between observational and interventional evidence. Cohort studies report hazard-ratio reductions of roughly 20–30%, whereas randomized trials of structured exercise report smaller and more heterogeneous effects on cognition [10,11]. Besides a true causal effect, several explanations may contribute to this gap: reverse causation (a long prodromal phase may reduce activity before diagnosis), residual confounding (for example by education, cognitive reserve, socioeconomic position, cardiometabolic disease, depression, and frailty), and selection

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bias (for example healthy-volunteer effects in large biobank cohorts). These issues are examined in Section 7.

Existing syntheses have mostly addressed either the effect of structured exercise on cognitive outcomes in randomized trials [10,11] or the weekend warrior pattern in relation to cardiovascular disease and mortality [7]. Among the sources identified in our search, we did not find a synthesis that appraises evidence on activity volume and pattern for dementia incidence alongside trial evidence, mechanistic plausibility, and practical prescription in one explicitly tiered framework. This review addresses that gap in narrative form; the limitations of that approach are set out in Section 7.6.

The aim of this narrative review is therefore threefold: (i) to summarize and critically appraise recent evidence on physical activity volume and distribution pattern in relation to dementia risk, distinguishing observational from interventional evidence and specifying the effect estimates on which conclusions rest; (ii) to appraise the biological hypotheses proposed to link exercise with brain health, distinguishing evidence from animal models from that available in aging humans; and (iii) to present a consensus-based, safety-conscious exercise prescription framework for heterogeneous older-adult populations, including those who are frail or functionally limited. These components rest on different kinds of evidence, which are kept distinct throughout (Figure 1): dementia-outcome evidence (Section 3) addresses the volume and pattern questions; mechanistic evidence (Section 4) addresses biological plausibility only; and the prescription framework (Sections 5 and 6) is derived from international consensus guidance rather than from the studies reviewed in Section 3, and is presented as practical translation, not as a finding of the review.

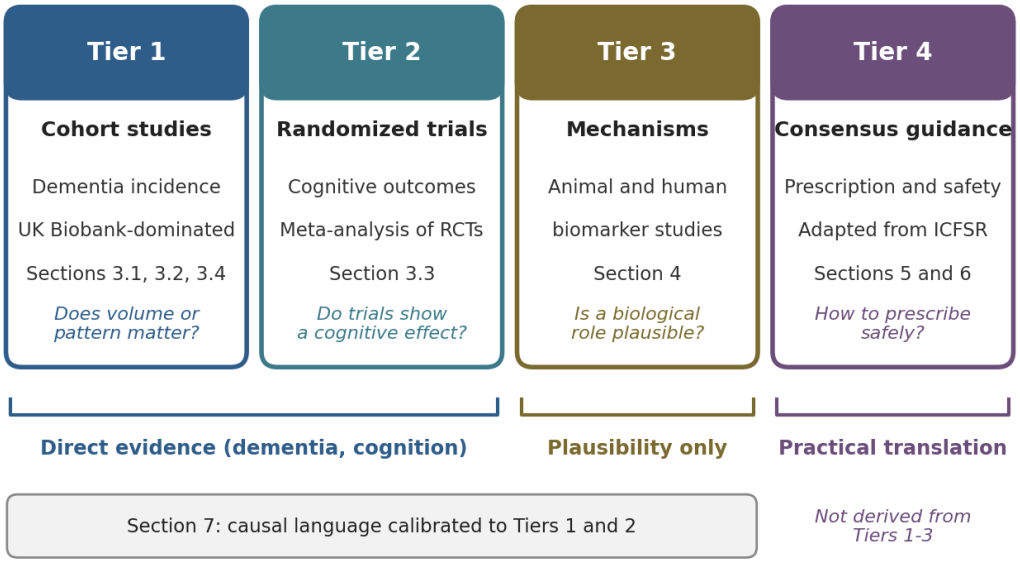

Figure 1. Conceptual framework of the review. The four evidence tiers answer different questions and are not interchangeable: only Tiers 1 and 2 bear directly on whether activity is associated with dementia risk or cognition; Tier 3 addresses plausibility; Tier 4 is consensus guidance and is not derived from Tiers 1–3.

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2. Methods

2.1 Study design and reporting framework

This manuscript is a narrative review prepared in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) [12]. SANRA is a reporting and quality-appraisal tool for narrative reviews and is not a substitute for systematic-review methodology. Accordingly, PRISMA 2020 reporting and PROSPERO registration were not applicable, no meta-analysis was performed, and no formal risk-of-bias tool was applied (see Sections 2.5 and 7.6).

2.2 Literature search strategy

Sources were identified by targeted searching of PubMed/MEDLINE for English-language publications from January 2015 to August 2026, supplemented by manual screening of the reference lists of eligible articles and of recent consensus statements. Search terms were combined with Boolean operators in three concept blocks, using the following PubMed syntax: (dementia[MeSH Terms] OR dementia[Title/Abstract] OR "Alzheimer disease"[MeSH Terms] OR "Alzheimer disease"[Title/Abstract] OR "cognitive decline"[Title/Abstract]) AND ("physical activity"[Title/Abstract] OR exercise[MeSH Terms] OR exercise[Title/Abstract] OR "exercise prescription"[Title/Abstract] OR "moderate-to-vigorous physical activity"[Title/Abstract] OR "light physical activity"[Title/Abstract] OR "weekend warrior"[Title/Abstract]) AND (prevention[Title/Abstract] OR "UK Biobank"[Title/Abstract] OR "healthy longevity"[Title/Abstract]), with filters English[Language] and 2015/01/01:2026/08/31[Date - Publication]. As is usual for a narrative review, searching was iterative and purposive rather than exhaustive, and the number of records retrieved was not recorded; no record counts are therefore reported.

PubMed/MEDLINE was chosen as the sole database because cohort studies with dementia endpoints, randomized trials, and consensus statements in clinical neuroscience and geriatrics are predominantly indexed there. This choice may have excluded relevant work indexed mainly in exercise-science, rehabilitation, psychology, or public-health databases (for example SPORTDiscus, PEDro, PsycINFO, Embase, Scopus, or Web of Science), and the restriction to English-language publications may have excluded further studies. These implications are discussed in Section 7.6; a multi-database search would be required for a systematic review.

2.3 Eligibility criteria

Inclusion criteria: peer-reviewed articles; prospective cohort studies, randomized controlled trials, systematic reviews/meta-analyses, or international consensus statements/guidelines; studies involving adults with a mean age of at least 50 years; studies reporting dementia incidence, cognitive decline, or validated cognitive outcomes, with quantified effect estimates where available.

Exclusion criteria: studies restricted to animal models without direct human translational data cited in the mechanistic section (animal studies are discussed only to characterize the level of evidence); conference abstracts, editorials, or opinion pieces without extractable primary data; and sources whose key bibliographic details (authorship, journal, year) or effect estimates could not be verified against the original publication. Where an estimate was available only graphically in the original publication, it is reported as not extracted (NR) and interpreted qualitatively.

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2.4 Study selection

Study selection was purposive rather than systematic. Titles and abstracts of retrieved articles were read by the authors, and potentially relevant articles were assessed in full text against the criteria in Section 2.3. Because no formal screening flow was conducted, duplicate independent screening was not performed and numbers of records screened and excluded are not reported; the consequences of this approach are discussed in Section 7.6. The evidence summarized in the text comprises five primary cohort analyses with dementia or mild-dementia outcomes (four in Table 1 and one further UK Biobank analysis), two systematic reviews with meta-analysis of randomized trials (one in Table 1), six sources on biological mechanisms, and two international consensus statements; further sources were used for background, epidemiology, and methodological context.

2.5 Data extraction and appraisal

Data were extracted from the original publications with AI assistance (see Disclosure of AI Assistance) and verified by the authors against the source texts, using a predefined form covering study design, sample size, follow-up, physical activity assessment method, outcome ascertainment, covariates adjusted, handling of reverse causation, and adjusted effect estimates (hazard ratios, standardized mean differences) with 95% confidence intervals, taken from the original publications. Particular attention was paid to how physical activity was ascertained, because the minute-based thresholds discussed in Section 3 are interpretable only with reference to measurement method; studies using wrist-worn accelerometry were distinguished from those relying on self-report. Physical activity intensity is described in conventional MET terms (LPA, approximately 1.6–2.9 METs; MVPA, ≥3.0 METs), but the included studies applied their own accelerometer classification algorithms (including machine-learning-based classification), so their minute thresholds may not map exactly onto MET categories.

No formal risk-of-bias tool was applied. Instead, each primary study was appraised qualitatively against five domains: exposure measurement, outcome ascertainment, confounder adjustment, handling of reverse causation, and independence from other included studies. These appraisals are reflected in Table 1 and Section 7, and the absence of a structured tool is acknowledged as a limitation (Section 7.6).

2.6 Evidence synthesis and evidence tiers

Given heterogeneity in study design, exposure ascertainment, outcome definition, and populations, quantitative pooling was not performed, and findings are synthesized narratively. To avoid presenting different kinds of evidence as if they had a common basis, four tiers are kept distinct throughout (Figure 1): Tier 1, observational cohort studies with dementia outcomes (Sections 3.1, 3.2, and 3.4); Tier 2, randomized-trial evidence on cognitive outcomes (Section 3.3); Tier 3, mechanistic evidence from animal and human biomarker studies (Section 4); and Tier 4, international consensus guidance (Sections 5 and 6). Only Tiers 1 and 2 bear directly on whether physical activity is associated with dementia risk or cognition.

3. Synthesis of evidence on physical activity and dementia risk

3.1 Volume and pattern of moderate-to-vigorous physical activity

The most directly relevant evidence comes from a UK Biobank analysis of 91,512 adults with a full week of wrist-accelerometer data (mean age 56 years at recruitment; median follow-up 8.6 years from accelerometry), in which dementia was ascertained from linked

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health records through April 2024 [4]. Compared with participants accumulating less than 150 min/week of MVPA, those accumulating 150–299 min/week did not show significantly lower dementia incidence (HR 0.94, 95% CI 0.79–1.12), whereas 300–599 min/week (HR 0.78, 95% CI 0.64–0.94) and ≥600 min/week (HR 0.61, 95% CI 0.45–0.83) did [4]. When participants were classified by pattern, those accumulating ≥300 min/week had lower dementia incidence than those accumulating less than 300 min/week, with HRs of 0.73 (95% CI 0.60–0.89) for a weekend-concentrated pattern (≥50% of MVPA within 1–2 days) and 0.79 (95% CI 0.64–0.98) for a regular pattern [4]. A direct comparison of the two patterns gave an HR of 0.91 (95% CI 0.70–1.18) [4]. Because this interval is wide and no equivalence margin was pre-specified, the data are compatible with comparable benefit but do not demonstrate equivalence.

Two further analyses of the same UK Biobank accelerometer sub-study compared weekend-concentrated activity (≥150 min/week with ≥50% of MVPA within 1–2 days) with inactivity (<150 min/week). One (n = 75,629; 530 incident dementia cases) reported an HR of 0.74 (95% CI 0.60–0.90) for the weekend pattern in a model adjusted for age and sex, corresponding to a 23% lower hazard in the fully adjusted model; the regular pattern was not significantly associated with dementia (HR 0.91, 95% CI 0.73–1.13, age- and sex-adjusted) [5]. The other (n = 92,144; 486 cases) reported a fully adjusted HR of 0.68 (95% CI 0.56–0.84) for the weekend pattern and a non-significant HR of 0.86 (95% CI 0.67–1.10) for a regular pattern [6]. A fourth analysis of the same sub-study reported lower dementia risk for the weekend pattern irrespective of sedentary time, whereas the regular pattern was associated with lower risk only among participants with shorter sedentary time [13].

These results are not fully concordant with Wang et al., in which the regular pattern was also protective [4]. A plausible contributor is that the three analyses defined “active” at different volumes and used different reference groups: Min et al. and Ning et al. defined activity at ≥150 min/week against an inactive group below 150 min/week, whereas Wang et al. required ≥300 min/week against a reference group below 300 min/week, and the 150–299 min/week range was not significantly protective in the dose–response analysis of Wang et al. [4–6]. Min et al. also reported that the association of the weekend pattern with dementia was attenuated and lost statistical significance after additional adjustment for total MVPA volume [5]. These differences should be resolved before minute-based thresholds are treated as fixed clinical targets.

Outside UK Biobank, a Mexican cohort (n = 10,033; mean age 51 years; 16 years of follow-up) used self-reported leisure-time exercise frequency and a Mini-Mental State Examination-based definition of mild dementia (2,400 cases). Compared with no exercise, the HR was 0.75 (95% CI 0.61–0.91) for exercising up to once or twice per week, 0.89 (95% CI 0.78–1.02) for exercising more often, and 0.84 (95% CI 0.75–0.95) for the two groups combined [14]. This supports the direction of the accelerometer findings, but its exposure (self-reported frequency rather than measured volume), outcome (screening-defined mild dementia rather than clinical dementia), and population differ.

3.2 Light physical activity

Among participants who did not meet the 300 min/week MVPA threshold, accumulating more than 840 min/week of LPA (about 2 hours/day) was associated with significantly lower all-cause dementia incidence than less than 420 min/week, whereas 420–839 min/week was not [4]. The hazard ratio for this comparison is displayed graphically in the source and is not available numerically in the main text; it is therefore recorded as not reported (NR) in Table 1 and is not interpreted quantitatively here. In the same analysis

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the association was not significant for Alzheimer's disease, and in stratified analyses it was significant in men, in the oldest age group (61–70 years), and in APOE ε4 carriers [4].

Three considerations call for caution. First, mean LPA in this cohort was approximately 2,100 min/week [4], so the 840 min/week cut-point lies well below the cohort average, and the contrast is likely to be driven by a small group with very low LPA who may differ in health status, which raises a reverse-causation concern. Second, the finding derives from one analysis of one cohort and, to our knowledge, has not been replicated with device-measured LPA in an independent cohort. Third, an analysis of UK Biobank based on self-reported activity was summarized by Wang et al. as showing the lowest dementia risk at around 209 min/week of LPA [4,15], a much lower volume, which illustrates how threshold values depend on the measurement method. The LPA finding is therefore best regarded as hypothesis-generating: it suggests that older adults who cannot reach moderate-to-vigorous intensities should not be excluded from prevention messaging, but it does not support a specific LPA target.

3.3 Randomized controlled trial evidence

In contrast to the hazard-ratio reductions of approximately 20–32% reported in the observational cohorts above, the principal systematic review and multilevel meta-analysis of randomized controlled trials of exercise interventions in adults over 50 years reported a considerably more modest pooled effect on global cognitive function (standardized mean difference 0.29, 95% CI 0.17–0.41), based on 39 trials [10]. Both aerobic and resistance modalities contributed to this effect, and effect sizes varied according to intervention duration, modality, and participant characteristics. These trials measure change in cognitive test performance over months, not incident dementia, and none of the studies summarized in this section is a randomized trial with dementia incidence as its primary endpoint. The observational–interventional discordance is discussed in Section 7.5.

3.4 Independence and consistency of the evidence

The three accelerometer-based dementia analyses summarized in Table 1 [4–6], and the fourth [13], all draw on the same UK Biobank accelerometer sub-study of approximately 103,000 wearers. Their analytic samples (75,629 to 92,144 participants) therefore overlap for the great majority of participants, and their findings are not independent confirmations. Consistency across them mainly shows that the result is robust to different definitions and covariate sets within one cohort, not that it generalizes to other populations. The same limitation applies to self-reported LPA findings from UK Biobank. For this reason the three main conclusions of this review are graded by the independence of their support:

- **>300 min/week MVPA threshold:** one cohort analysis [4]. A Japanese cohort using self-reported activity has been reported, as summarized by Wang et al., to show lower risk of suspected dementia at ≥300 min/week of moderate activity [16]. The threshold should be treated as a hypothesis, not a clinical target.
- **Concentrated versus regular pattern:** four non-independent UK Biobank analyses and one independent cohort with self-reported activity and a different outcome [14]. Direction is consistent; precision for the head-to-head comparison is limited.
- **LPA >840 min/week:** one analysis of one cohort [4], with the numerical estimate not available.

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Table 1. Summary of key primary studies discussed in this review (Tiers 1 and 2)

Study	Cohort, design, and follow-up	Physical activity assessment	Comparison (exposure vs reference)	Adjustment and bias handling	Effect estimate (95% CI)
[4]	UK Biobank prospective cohort; n = 91,512; mean age 56 y at recruitment; median follow-up 8.6 y from accelerometry (15.3 y from recruitment); dementia from linked health records to April 2024; case counts in the source's supplementary tables (not extracted)	Wrist accelerometer, 7 days; UK Biobank-derived MVPA minutes; LPA from the same device	MVPA vs <150 min/week: 150–299 min/week 300–599 min/week ≥600 min/week	Age, sex, education, ethnicity, deprivation, smoking, alcohol, diet, diabetes, hypertension, heart attack, stroke, BMI, LPA; sensitivity analysis excluding dementia within 2 y of accelerometry (similar results)	HR 0.94 (0.79–1.12) HR 0.78 (0.64–0.94) HR 0.61 (0.45–0.83)
[4]	Same cohort	Accelerometer MVPA	≥300 min/week MVPA, ≥50% in 1–2 days (weekend-concentrated) vs <300 min/week ≥300 min/week MVPA, regular pattern vs <300 min/week Weekend-concentrated vs regular (direct)	As above	HR 0.73 (0.60–0.89) HR 0.79 (0.64–0.98) HR 0.91 (0.70–1.18)
[4]	Same cohort; participants with <300 min/week MVPA	Accelerometer LPA	LPA >840 min/week vs <420 min/week (420–839 min/week not significant)	As above, plus total MVPA	Significantly lower all-cause dementia incidence; HR shown graphically only (NR). Not significant for Alzheimer's disease
[5]	UK Biobank; n = 75,629; mean age 61.8 y; median follow-up 8.4 y; 530 dementia cases	Wrist accelerometer; machine-learning MVPA classification	Weekend warrior (≥150 min/week, ≥50% in 1–2 days) vs inactive (<150 min/week) Regular (≥150 min/week) vs inactive	Fully adjusted model: 13 covariates including sleep, diet, BMI, comorbidity; sensitivity analyses excluding events in first 1 and 2 y	Age- and sex-adjusted HR 0.74 (0.60–0.90); fully adjusted: 23% lower hazard HR 0.91 (0.73–1.13), age- and sex-adjusted, not significant

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Study	Cohort, design, and follow-up	Physical activity assessment	Comparison (exposure vs reference)	Adjustment and bias handling	Effect estimate (95% CI)
[6]	UK Biobank; n = 92,144; median follow-up 8.85 y; 486 dementia cases	Wrist accelerometer; machine-learning MVPA classification	Weekend warrior (≥150 min/week, ≥50% in 1–2 days) vs inactive Regular vs inactive	Age, sex, ethnicity, deprivation, education, employment, smoking, alcohol, diet, comorbidity; first 2 y excluded; 5-y exclusion in sensitivity analysis	HR 0.68 (0.56–0.84) HR 0.86 (0.67–1.10), not significant
[14]	Mexico City Prospective Study; n = 10,033; mean age 51 y; 16 y follow-up; 2,400 cases of mild dementia (MMSE ≤22)	Self-reported leisure-time exercise frequency	Exercise up to 1–2 times/week (weekend warrior) vs none More frequent exercise vs none Combined vs none	Adjusted for confounders (see source)	HR 0.75 (0.61–0.91) HR 0.89 (0.78–1.02) HR 0.84 (0.75–0.95)
[10]	Systematic review with multilevel meta-analysis of 39 RCTs; adults >50 y	Structured exercise interventions (aerobic and/or resistance)	Exercise vs control	Not applicable (randomized trials)	Global cognition: SMD 0.29 (0.17–0.41)

HR, hazard ratio; CI, confidence interval; MVPA, moderate-to-vigorous physical activity; LPA, light physical activity; SMD, standardized mean difference; BMI, body mass index; MMSE, Mini-Mental State Examination; NR, numerical estimate not reported in the main text of the source. The first three rows, and the rows for Min et al. and Ning et al., use overlapping UK Biobank accelerometer data (Section 3.4). Reference groups differ between studies (<150 vs <300 min/week MVPA), so estimates are not directly comparable. Cohort sizes, follow-up, and covariates are taken from the original publications.

4. Biological mechanisms: species and evidence-level considerations

This section appraises mechanistic hypotheses (Tier 3). It addresses biological plausibility only and cannot establish that exercise prevents dementia. The pathways below were selected because they are among the most frequently proposed mediators between exercise and brain health and because human data exist for at least some of them; the selection is therefore not exhaustive. Other pathways, for example anti-inflammatory effects, sleep, amyloid and tau processing, and glymphatic function, are outside the scope of this review and may be equally important. Table 2 summarizes the level of evidence for each pathway by species.

4.1 Cerebrovascular and metabolic pathways

Aerobic exercise improves cardiorespiratory fitness, endothelial function, and glucose–insulin regulation, all of which are plausible contributors to cerebrovascular health and to the vascular contribution to cognitive decline; vascular and metabolic risk factors are among the modifiable factors identified by the Lancet Commission [3]. This pathway rests on the broad general cardiovascular physiology literature, which this review does not itemize, and is treated as established background physiology rather than dementia-specific evidence.

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4.2 Neurotrophic signaling and hippocampal neurogenesis

Animal models point to a key role for brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) in mediating exercise-induced hippocampal change. Human evidence is weaker. In an exercise-intervention study in older adults using MRI and serum biomarkers, peripheral BDNF, IGF-1, and VEGF levels were not significantly affected by exercise, and their changes were not related to changes in fitness or hippocampal perfusion; changes in IGF-1 correlated with hippocampal volume change and verbal recall, but independently of exercise [17]. Whether adult hippocampal neurogenesis persists in the aging human brain is itself contested, with studies reporting opposing findings [18,19]. This review therefore treats BDNF signaling and exercise-induced hippocampal neurogenesis as hypotheses supported in rodents but not established in the aging human brain.

4.3 Muscle-derived signaling (myokines): irisin/FNDC5, cathepsin B, and interleukin-6

Irisin, cleaved from the membrane protein FNDC5 and released by skeletal muscle during exercise, has been proposed as a mediator of muscle–brain crosstalk. In experimental Alzheimer's disease mouse models, knockdown of brain FNDC5/irisin impaired synaptic plasticity and memory, while restoring FNDC5/irisin expression rescued these deficits; the same study also reported reduced FNDC5/irisin levels in the hippocampus and cerebrospinal fluid of individuals with Alzheimer's disease [20]. The evidence is substantially stronger and more mechanistically detailed in rodents than in humans, where the corresponding data are chiefly correlational (reduced levels in disease) rather than interventional.

Cathepsin B is a second candidate. In mice, running increased muscle and plasma cathepsin B, and running did not enhance hippocampal neurogenesis or spatial memory in cathepsin B knockout mice; treadmill exercise elevated plasma cathepsin B in rhesus monkeys and humans, and in humans changes in cathepsin B correlated with fitness and hippocampus-dependent memory [21]. The human data are correlational, and the role of cathepsin B in the brain is debated. Interleukin-6 is released by contracting skeletal muscle and has been proposed as a myokine with systemic metabolic and anti-inflammatory signaling effects [22]; its actions are context-dependent, and we did not identify direct human evidence that exercise-induced muscle interleukin-6 mediates cognitive benefit.

4.4 Frailty and musculoskeletal pathways

Resistance exercise supports skeletal muscle mass and strength, which are inversely associated with frailty; because frailty is itself an independent correlate of cognitive decline, preservation of muscle function is a plausible indirect pathway linking exercise to cognitive outcomes, distinct from the more direct neurotrophic and vascular pathways discussed above.

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Table 2. Level of evidence for proposed mechanisms linking exercise with brain health, by species (Tier 3)

Pathway / mediator	Animal or preclinical evidence	Human evidence	Level of evidence for a role in dementia prevention (authors' qualitative appraisal)
Cerebrovascular and metabolic pathways	Not specific to dementia	Exercise improves cardiorespiratory fitness, endothelial function, and glucose regulation; link to dementia is indirect [3]	Moderate, indirect
BDNF and hippocampal neurotrophic signaling	Robust in rodent models [17]	Inconsistent; peripheral BDNF, IGF-1, and VEGF not significantly changed by exercise in one older-adult study [17]	Limited, inconsistent
Adult hippocampal neurogenesis	Established in rodents	Contested in adult and aging human brain [18,19]	Not established in humans
Irisin/FNDC5	Rescue of synaptic and memory deficits in Alzheimer's mouse models [20]	Reduced levels in Alzheimer's hippocampus and cerebrospinal fluid (correlational) [20]	Preliminary
Cathepsin B	Knockout abolishes running-induced neurogenesis and memory gains in mice [21]	Plasma levels rise with exercise; correlate with fitness and memory (correlational) [21]	Preliminary; role debated
Interleukin-6	Released by contracting muscle; effects context-dependent [22]	No direct evidence identified of mediation of cognitive benefit	Inconclusive
Frailty and musculoskeletal pathways	Not applicable	Muscle mass and strength inversely associated with frailty; frailty correlates with cognitive decline	Indirect; plausible

BDNF, brain-derived neurotrophic factor; IGF-1, insulin-like growth factor-1; VEGF, vascular endothelial growth factor; FNDC5, fibronectin type III domain-containing protein 5. The levels of evidence are qualitative appraisals by the authors, not the output of a formal evidence-grading system.

5. From evidence to practice: a consensus-based exercise prescription framework

This section moves from the findings of the review to practical translation, and two evidentiary bases must be kept apart. The dementia-outcome evidence in Section 3 supports only a limited set of statements about volume and pattern (that higher MVPA volumes, and possibly higher LPA volumes, are associated with lower dementia incidence); it was not designed to specify modality, intensity, progression, or safety parameters. The detailed parameters in Table 3 derive from international consensus recommendations for older adults [23,24], which draw on broader evidence on physical function, frailty, falls, and chronic disease and reflect expert judgement. They are not outputs of the evidence synthesis in Section 3, and no study in Section 3 tested this framework against dementia endpoints.

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The consensus statements recommend individualized, multicomponent prescriptions combining aerobic, resistance, balance, and dual-task training rather than a single-modality approach [23,24]. Table 3 summarizes a practical framework adapted by the authors from these documents for three broad older-adult profiles; it has not been validated as a dementia-prevention intervention. Where the aerobic volumes in Table 3 overlap with the cohort thresholds in Section 3, the correspondence is not derived, and the >300 min/week threshold from a single cohort should not be read as a prescription. Individual prescriptions should be set by a qualified exercise or health professional on the basis of comprehensive assessment.

Table 3. Consensus-derived multicomponent exercise prescription framework (FITT-based): a practice guide, not a result of the evidence synthesis (Tier 4)

Component	Healthy community-dwelling older adults	Frail / multimorbid older adults	Mobility-limited or MCI
Aerobic exercise	150–300 min/week moderate intensity, or 75–150 min/week vigorous intensity; progress gradually	Start at lower end of range; short bouts (e.g., 5–10 min), interval-style; monitor exertion (RPE 11–13/20)	Emphasize accumulated light-to-moderate activity if MVPA not tolerated; seated or supported aerobic options
Resistance training	2–3 sessions/week, non-consecutive days; 1–3 sets of 8–12 repetitions per major muscle group; moderate-to-high intensity, progressing toward ~60–80% of 1-repetition maximum or an equivalent perceived-effort target where 1RM testing is not feasible	2 sessions/week; lower initial load (RPE-guided); emphasis on functional movements (sit-to-stand, step-ups)	Chair-based or supported resistance exercises; focus on lower-limb strength for transfer and gait safety
Balance training	2–3 sessions/week; progressive challenge to postural control	Included in every session; supervised initially given elevated falls risk	Supervised, individually tailored; may require assistive support
Cognitive-motor dual-task training	1–2 sessions/week combining physical and cognitive demands (e.g., stepping with counting tasks)	Simplified dual-task paradigms; close supervision	Adapted to residual motor and cognitive capacity
Flexibility	2–3 sessions/week, major muscle-tendon groups	As tolerated; gentle range-of-motion work	Passive or assisted stretching as appropriate

1RM, one-repetition maximum; RPE, rating of perceived exertion (Borg 6–20 scale); MCI, mild cognitive impairment. Adapted from consensus recommendations [23,24]; intensity and progression parameters should be individualized and supervised by a qualified professional.

6. Safety considerations and risk stratification

This section is intentionally brief. It is included because exercise prescription cannot responsibly be separated from safety, and, like Section 5, it reflects consensus guidance and clinical practice rather than findings of the evidence review [23,24]. Implementation of exercise prescription in older adults, particularly those who are frail, cognitively impaired, or living with cardiometabolic comorbidity, requires structured safety measures:

- Pre-participation screening for cardiovascular, orthopedic, and neurological contraindications before initiating moderate-to-vigorous intensity programs, with medical clearance sought where risk factors are present.
- Falls-risk assessment prior to prescribing balance or resistance training in frail or cognitively impaired individuals, given the elevated baseline falls risk in this population.
- Supervision by qualified professionals (physiotherapists, clinical exercise physiologists) during initial sessions for higher-risk participants, transitioning to semi-supervised or independent activity as tolerance is established.

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- Explicit contraindications and relative contraindications (e.g., uncontrolled arrhythmia, unstable angina, severe orthopedic instability, acute illness) should be documented before program initiation.
- Gradual progression of intensity, volume, and complexity, with regular reassessment, to minimize overuse injury and adverse cardiovascular events.
- Structured adverse-event monitoring and reporting should be embedded in any community or clinical exercise program for older adults, both for individual safety and to build the evidence base on real-world program safety, which is presently underreported in the literature reviewed here.

7. Discussion and conclusions

7.1 Principal findings and evidentiary weight

Taken together, the dementia-outcome evidence indicates that higher accelerometer-measured MVPA volumes are associated with lower dementia incidence in UK Biobank, and that concentrating this activity into one or two days is not associated with a clearly different risk from distributing it. This conclusion rests mainly on one cohort (Section 3.4), on observational design, and on a single baseline week of accelerometry, which may not represent habitual activity patterns over years. The specific thresholds (>300 min/week of MVPA; >840 min/week of LPA) each come from a single analysis and should not be treated as fixed clinical targets.

7.2 Calibrating causal language to an observational evidence base

The central quantitative findings of this review derive overwhelmingly from prospective observational cohorts. These associations should be described as such rather than as demonstrated causal or preventive effects. This distinction is not a semantic nicety: the hazard-ratio reductions reported in cohort studies (approximately 20–32%) are considerably larger than the modest pooled cognitive effect observed in randomized trials [10], and the reasons for this gap require sustained discussion rather than a single qualifying sentence.

7.3 Reverse causation

Dementia has a long prodromal phase, often spanning a decade or more, during which subtle behavioral and motor changes can reduce physical activity before a formal diagnosis is made. Lower activity among individuals who later develop dementia may therefore partly reflect early, subclinical disease. The cohort analyses in Table 1 applied some mitigation: Wang et al. repeated their analysis excluding dementia diagnosed within 2 years of accelerometry, with similar results [4]; Min et al. excluded events in the first 1 and 2 years of follow-up [5]; and Ning et al. excluded the first 2 years and, in a sensitivity analysis, the first 5 years, in which results were less stable at the ≥300 min/week threshold [6]. Given a prodromal phase of a decade or more and median follow-up of roughly 8–9 years from accelerometry, exclusions of 1–5 years can reduce but not eliminate this bias, and none of the analyses had repeated activity measurements with which to examine changes in activity before diagnosis.

7.4 Residual confounding and healthy-volunteer selection bias

The cohort analyses adjusted for sociodemographic factors, lifestyle, and comorbid conditions (Table 1), but unmeasured or imprecisely measured factors, including cognitive reserve beyond educational attainment, depression, sleep quality, and baseline frailty,

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may influence both activity and dementia risk, so residual confounding remains a plausible explanation for part of the observed associations. APOE ε4 status was not included in the primary models of Wang et al. because genotype data were missing for part of the sample, and the association was significant only among non-carriers in their stratified analyses [4].

A further source of bias affecting all UK Biobank-derived estimates is healthy-volunteer selection: participants are older, less socioeconomically deprived, and healthier than the source population, with lower all-cause mortality and disease incidence [25], and the accelerometer sub-study required additional agreement to participate [5]. This may attenuate or otherwise distort exposure–outcome associations and limits generalizability. The cohorts were also predominantly White (about 97% in Wang et al.) and middle-aged to older (mean age about 62 years at accelerometry in the analyses of Min et al. and Ning et al.), so the findings may not apply to the oldest age groups, more diverse populations, or those with greater comorbidity or lower baseline activity [4,5].

7.5 Reconciling observational and interventional evidence

The gap between large cohort-study hazard ratios and the modest randomized-trial effect size [10] may partly reflect genuine differences between decades of cumulative habitual activity, as captured in cohort exposure measures, and relatively short (typically 3–12 month) structured interventions; partly reflect the biases discussed above operating on the observational estimates; and partly reflect that trials, by design, cannot capture activity patterns sustained across a lifetime. This review does not attempt to adjudicate the relative contribution of each explanation, since doing so would require pooled analysis beyond the scope of a narrative synthesis, but it treats the discordance as a central, unresolved feature of this evidence base rather than a minor caveat.

7.6 Strengths and limitations of this review

A strength of this review is that every quantitative estimate is traceable to a named source, extracted from the original publication, and flagged where a numerical estimate was unavailable. Its principal limitations are: the narrative (non-systematic) design, which does not permit formal risk-of-bias grading or pooling; reliance on a single database (PubMed/MEDLINE) and on English-language publications, which may have missed relevant studies indexed elsewhere; purposive, non-systematic study selection without a recorded screening flow or duplicate screening, which may introduce selection bias; substantial overlap of the UK Biobank data source across the primary cohort analyses in Table 1, which limits their independence as corroborating evidence; the non-exhaustive selection of mechanistic pathways; and a prescription framework that is consensus-derived and has not been tested against dementia endpoints. Evidence on thresholds is further limited by differences between studies in activity definitions, reference groups, and accelerometer classification algorithms.

7.7 Future research priorities

Priority areas for future research include: large pragmatic randomized trials of flexible, volume-based exercise prescriptions with dementia or validated cognitive endpoints and follow-up exceeding the typical 3–12 month intervention window; replication of the volume and pattern findings in cohorts outside UK Biobank with device-measured activity, repeated activity measurements, and pre-specified equivalence margins for pattern comparisons; explicit application and reporting of lag or landmark analyses in observational cohorts to address reverse causation; recruitment strategies or statistical reweighting methods to reduce healthy-volunteer bias; verification of the light-physical-activity association with fully reported effect estimates; and mechanistic studies in humans

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designed to test, rather than assume, the translational relevance of rodent-model myokine and neurotrophic pathways.

7.8 Conclusions

Higher weekly physical activity volume is associated with lower dementia incidence in accelerometer-based cohorts, and the available comparison does not show a clear difference between concentrating activity into one or two days and distributing it more evenly. These findings come mainly from one cohort and from observational data subject to reverse causation, residual confounding, and healthy-volunteer selection bias, and randomized trials show a more modest effect on cognition. Supervised, multicomponent exercise consistent with international consensus guidance is a reasonable and low-risk recommendation for older adults, but should be presented as a probable contributor to risk reduction rather than a proven preventive therapy, pending confirmatory trials with dementia-relevant endpoints and longer follow-up.

Declarations

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Conflicts of Interest

The authors declare no conflict of interest.

Ethics Statement

This article is a narrative review and does not involve human subjects, primary data collection, or experimental procedures; ethical approval was therefore not required.

Data Availability Statement

This review did not generate new primary data. All quantitative findings reported in Table 1 are drawn from the published sources cited in the reference list; the underlying UK Biobank data referenced by the primary studies are available to registered researchers through UK Biobank's standard data-access procedure and are not held by the present authors.

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