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REVIEW ARTICLE

Systematic review and meta-analysis on population attributable fraction for physical inactivity to dementia

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Abstract

INTRODUCTION: The number of cases of dementia attributable to physical inactivity remains unclear due to heterogeneity in physical inactivity definitions and statistical approaches used.

METHODS: Studies that used population-based samples to estimate the population attributable fraction (PAF) of physical inactivity for dementia were included in this review. Weighted PAFs were adjusted for communality among the risk factors (i.e., inactive persons may also share other risk factors) analyzed. Values were reported as percentage (%) of cases of dementia attributable to physical inactivity.

RESULTS: We included 22 studies. The overall impact of physical inactivity, defined by any criteria, on dementia ranged from 6.6% (95% CI: 3.6%, 9.6%; weighted) to 16.6% (95% CI: 14.4%, 18.9%; unweighted). Studies using the WHO criterion for physical inactivity estimated a higher unweighted impact ($\beta = 7.3\%$; 95% CI: 2.0%, 12.6%) than studies using other criteria.

DISCUSSION: Conservatively, one in 15 cases of dementia may be attributable to physical inactivity, defined by any criteria.

KEYWORDS
dementia, physical inactivity, population attributable fraction

1 | INTRODUCTION

Dementia is a leading cause of death and disability worldwide.[1] The increasing incidence, especially in low- and middle-income countries, highlights the urgent need for well-coordinated strategies to control the present and reduce the future burden of dementia.[2–4] Although population aging is expected to lead to increases in projected dementia cases worldwide,[4] previous investigations showed that approximately 40% of all cases of dementia in the world could be attributable to 12 modifiable risk factors: low education, depression, smoking, air pollution, traumatic brain injury, excessive alcohol consumption, type 2 diabetes, hypertension, obesity, social isolation, hearing impairment, and physical inactivity.[5] These findings are significant as they provide public health agencies with directions to effectively reduce the incidence of dementia.

The population attributable fraction (PAF) is the proportion of cases for an outcome (in this case, dementia) attributable to a particular exposure (physical inactivity).[6] It is estimated using Levin's formula, based on the prevalence of the risk factor (P) and the relative risk (RR) of the association between exposure and outcome. Also, the communality is calculated to account for overlapping across risk factors (for example, inactive persons also may have diabetes). The communality is also used to estimate the combined PAF of several risk factors (Panel S1). The PAF estimates the impact of a theoretical reduction in the prevalence of one or more exposures on the disease incidence. For example, Lee et al.[7] showed that almost 10% of all deaths worldwide in 2008 were attributable to physical inactivity. Oliveira et al.[8] demonstrated that reducing by 20% the prevalence of seven risk factors (physical inactivity, diabetes, hypertension, obesity, depression, smoking, and low education) per decade could reduce the prevalence of dementia by up to 19.5% in 2050 in Mozambique, Brazil, and Portugal.

However, heterogeneity in defining a risk factor may underestimate or overestimate its association with a given outcome. For example, the PAF estimated for physical inactivity on dementia has ranged from 6.5%[5] to 30.7%[8] in previous studies. Norton et al.[9] used the World Health Organization (WHO) definition of physical inactivity (less than 150 min of moderate-to-vigorous physical activity per week)[10] to show that one in five cases of dementia in the USA, UK, and Europe was attributable to physical inactivity. However, Mukadam et al.[11] found a lower PAF in India: 8.4%. Besides the regional difference, the authors defined physical inactivity as "not at all" or "not very physically active" on a Likert scale by self-report. Thus, the use of different instruments for assessing inactivity and discrepancies in definitions of inactivity and statistical approaches (unweighted vs. weighted) have led to inconsistent estimates, and it remains unclear what the true impact of inactivity on dementia might be. Therefore, this study aimed to estimate the number of cases of dementia attributable to physical inactivity, under various conditions.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors used PubMed and Web of Science sources to review the literature. We did not find any systematic review or meta-analysis that examined the population attributable fraction (PAF) of physical inactivity to the burden of dementia. Also, previous cohort studies examining the PAF of physical inactivity have provided discrepant results.
2. **Interpretation**: Our findings conservatively showed that 7% of cases of dementia worldwide could be attributable to physical inactivity. Studies using the World Health Organization criterion of physical inactivity revealed a higher attributable fraction. Studies using different datasets to calculate attributable fractions and communality estimated lower PAF than those using the same source. Heterogeneity among studies was the most important factor associated with a wide range of PAF of physical inactivity and dementia.
3. **Future directions**: Future studies must prioritize, when feasible, validated and widely recognized criteria for physical inactivity to estimate the burden of dementia attributable to physical inactivity precisely. PAF of physical inactivity may be calculated from population-based studies with longitudinal data acquisition to clarify the impact of physical inactivity on dementia.

2 | METHODS

2.1 | Search strategy

We systematically reviewed the studies published in journals indexed in two large databases: PubMed and Web of Science. Studies were searched from the inception of the databases to October 15, 2022, with no language restrictions. The terms used in the search were related to physical inactivity, dementia, and PAF. The detailed search strategies are described in Table S1. This systematic review is registered in PROSPERO (CRD42022375169) and follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[12]

2.2 | Eligibility criteria

We included original articles and systematic review studies that estimated the PAF of physical inactivity for dementia in population-based samples. There were no restrictions to time and measurements. We included articles written in English, Spanish, or Portuguese only. Titles and abstracts were screened by four independent reviewers (NF, JSL, JC, LSS). Then, the full-text articles were read and selected based on inclusion and exclusion criteria. There were no disagreements among reviewers.

2.3 | Data collection process

The reviewers independently extracted the following information from the included articles: country or region, physical activity measurement, physical inactivity definition, the RR used for the association between physical inactivity and dementia, country's income, study design, and the combined and physical inactivity-specific PAF with dementia. Two types of PAFs were reported in the included studies. Unweighted PAFs are calculated using the prevalence and RR of physical inactivity only. Weighted PAFs included communality in the formula, which accounted for overlap with other risk factors for dementia (Panel S1). The exact unweighted and weighted PAFs were extracted from the included studies.

2.4 | Risk of bias assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of evidence.[13] This scale comprises eight items related to study selection, comparability, and outcome. For cohort studies, the original version of the NOS scale was used; for cross-sectional studies, we used an adapted version from the actual scale based on a previous publication.[13] Under NOS, a study received one star if classified as high quality for each item, except for the outcome item, which scored two stars if independent blind assessments or record linkage were used to examine the outcome. The total NOS score varies from 0 to 9 for cohort studies and from 0 to 8 for cross-sectional studies. Publication bias was assessed using visual inspection of contour-enhanced funnel plots and statistically by Egger's regression test (Figure S1).

2.5 | Effect measures and synthesis methods

We meta-analyzed the PAF of physical inactivity from the included studies using random effect models due to high methodological heterogeneity. Values were reported as a percentage (%) of cases of dementia attributable to dementia. Heterogeneity was assessed using the chi-squared (Q) and I^2 statistics. An I^2 statistic $>$ 50% indicated large heterogeneity between studies.

Subgroup meta-analysis and meta-regression were then performed according to (1) physical inactivity definition, (2) the RR used for the association between physical inactivity and dementia, (3) world region, (4) country's income, (5) study design, and (6) the communality between physical inactivity and other modifiable risk factors. These analyses investigate the association between the studies' characteristics and the estimated effect sizes. In meta-regression, we identified possible sources of heterogeneity, with a positive coefficient indicating that the covariate category (or definition) was associated with a higher PAF. The random-effects meta-regression used residual restricted maximum likelihood to measure between-study variance. Multivariable meta-regression models were constructed based on the proportion of variance explained by the model (R^2). When all covariates were analyzed together, permutation tests were performed ($n = 1000$) to address the issue of multiple testing by calculating adjusted p-values. Analyses were performed using the Meta package through the R programming language.[14]

Finally, we calculated the best estimate of the proportion of cases of dementia attributable to physical inactivity under these standard conditions. We estimated the prevalence of physical inactivity for each country, defined as not fulfilling WHO criteria, from the WHO's Global Health Observatory.[15] We used the adjusted RR of 1.4, based on the 2020 Lancet Commission on Dementia.[5] The PAF was calculated using Levin's formula (Panel S1) that accounted for the communality of inactivity with other risk factors for dementia. The dataset and scripts used to perform this study are available at https://osf.io/wt3ja/?view_only=231ff60bc3854b0c9afb6307a02e0a90.

3 | RESULTS

3.1 | Study selection and characteristics

We included 22 studies in the present review (Figure 1), of which only two were prospective cohort studies.[16,17] Most studies included adults from Latin America [8,11,18–22] (k = 7) (Table 1).[23–25] Samples ranged from 565[16] to 250,000 participants.[26] Four studies performed a systematic review to identify the PAF of physical inactivity for dementia based on cross-sectional estimates.[5,8,27,28] Physical inactivity was assessed by self-report questionnaires in all studies.

Studies used different criteria to define physical inactivity. The most common definition (65%) used the WHO criteria. The median prevalence of physical inactivity, defined using individual study-specific criteria, was 34.2%, ranging from 9.3% (Mozambique)[8] to 82.2% (China).[26] Most PAFs were calculated using RRs for the association between physical inactivity to dementia of 1.82 (95% confidence interval [CI]: 1,19, 2.78)[8,9,19] or 1.4 (95% CI: 1.2, 1.7).[20,21,26,29–31] Four studies did not calculate the PAF accounting for the communality of inactivity with other risk factors for dementia.[16,17,19,26] We also observed that 48% of the weighted PAFs were estimated using different data sources to calculate the prevalence of physical inactivity and the communality across risk factors.[5,8,9,21,27,29,31] For example, some studies calculated the prevalence of physical inactivity using data from low- and middle-income countries and communality from high-income countries. Consequently, the studies showed a wide range of communality calculated among the risk factors, ranging from 27% to 78%.

3.2 | Meta-analysis

We found an unweighted PAF (i.e., that did not account for communality of risk factors) of physical inactivity, defined by any criteria, for dementia of 16.6% (95% CI: 14.4%, 18.9%) (Figure 2A). The highest and lowest unweighted PAFs were observed in Portugal (30.5%) and Mozambique (7.1%), respectively (Figure 3A). As expected, the weighted PAF (accounting for communality) was lower (6.6%; 95% CI: 3.6%, 9.6%) (Figure 2B) than the unweighted PAF.

Studies using the WHO definition showed slightly higher values than studies using other criteria to classify subjects as physically active or not (Table 2). As expected, a higher RR (i.e., using 1.82 compared with 1.4) was associated with higher PAF across the included studies. Studies using the same dataset (i.e., the same population) to calculate the prevalence of physical inactivity and communality across different risk factors estimated higher PAF than studies that estimated prevalence and communality from different sources. Some studies combined the weighted PAFs for several modifiable risk factors to estimate the total

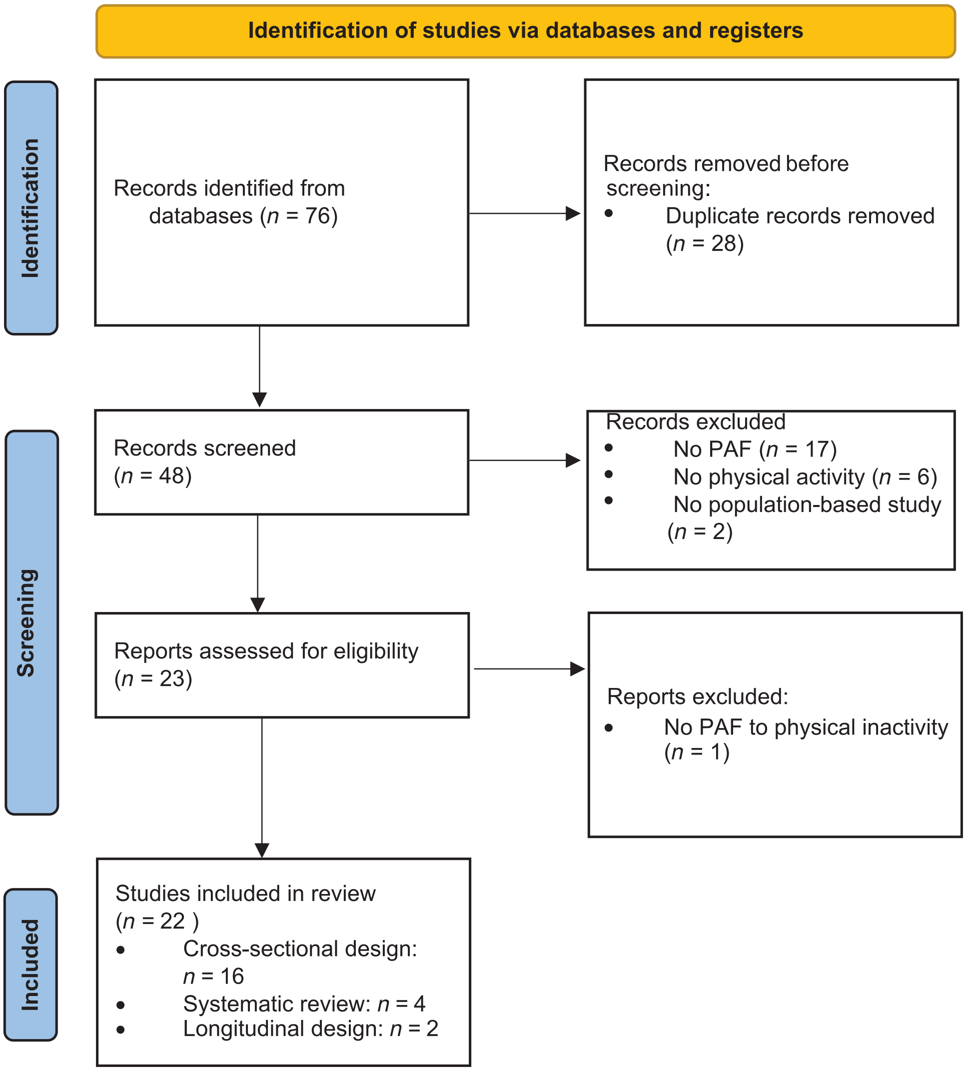

FIGURE 1 Flowchart of the selection of studies. PAF, population attributable fraction

number of cases of dementia potentially preventable by controlling risk factors such as physical inactivity, diabetes, hypertension, and depression. A higher proportion of preventable cases was observed in studies from Chile (56.0%), Barbados (50.9%), and Brazil (50.5%) (Figure 3B).

3.3 | Meta-regression

No covariate level or definition was associated with a significantly higher unweighted PAF compared with other levels/definitions in the univariate meta-regression (Table S2). The model that best explained the heterogeneity of unweighted PAF included physical inactivity definition and country region (R^2 = 35%) (Table S3). In the multivariate model, studies using WHO criteria for physical inactivity obtained higher PAFs than those using other criteria (β = 7.28%; 95% CI: 2.00%, 12.56%) (Figure 4A and Table S4). Values were consistent after 1000 permutation tests (Table S5).

In univariate analysis, only the RR was significantly associated with the weighted PAF (Table S2). The model with countries' income, RR, communality, prevalence source, and the physical inactivity definition best explained the heterogeneity of the findings (R^2 = 89%) (Table S3). We observed an inverse relationship between communality and PAF, with higher communality associated with lower PAF, as expected (Figure 4B and Table S4). Studies in which communality and physical inactivity prevalence were calculated using the same dataset showed higher PAF than studies that estimated them using different sources (β = 8.15%; 95% CI: 2.28, 14.02). Finally, studies using WHO criteria for physical inactivity obtained higher PAFs than those using other criteria, although this was not statistically significant (β = 4.50%; 95% CI: –0.29%, 9.29%, p = 0.066). Only RR remained associated with weighted PAF after permutation tests (Table S4).

3.4 | Risk of bias

Although our funnel plot showed an asymmetry to the right (Figure S1), Egger's test for unweighted (p = 0.247) and weighted PAF

TABLE 1 Characteristics of the included studies

Authors	Country	PA measure	Physical inactivity cut-off	Physical inactivity prevalence	RR for dementia	Communality	Unweighted PAF for physical inactivity	Weighted PAF for physical inactivity[b]	Overall PAF for non-modifiable RF
Norton et al. (2014)	USA	SR	At least moderate PA 5x p/week, 30 min p/day OR at least vigorous PA 3x p/week, 20 min p/day	32.5%	1.82 (1.19, 2.78)	49.0%	21.0%	–	52.7% and 30.6%[b]
Norton et al. (2014)	UK	SR	Same as above	34.0%	1.82 (1.19, 2.78)	49.0%	21.8%	–	52.0% and 30.0%[b]
Norton et al. (2014)	Europe	SR	Same as above	31.0%	1.82 (1.19, 2.78)	49.0%	20.3%	–	54.0% and 31.4%[b]
Norton et al. (2014)	World	SR	Same as above	17.7%	1.82 (1.19, 2.78)	49.0%	12.7%	–	49.4% and 28.2%[b]
Livingston et al. (2017)	World	SR		17.7%	1.4 (1.16, 1.67)	26.6%	6.5%	2.6%	35%[b]
Livingston et al. (2020)	World	SR		17.7%	1.4 (1.2, 1.7)	55.2%	9.6%	1.6%	40%[b]
Wyllians et al. (2022)	Brazil	SR (IPAQ)	< 3 days p/week of walking or exercise	47.2%	1.4 (1.2, 1.7)	29.0%	15.9%	11.3%	50.5%
Mukadam et al. (2019)	Latin America	SR (Four-point Likert scale)	Not at all or not very physically active	34.2%	1.4 (1.2, 1.7)	37.0%	17.0%	4.5%	55.8%
Mukadam et al. (2019)	China	SR (Four-point Likert scale)	Same as above	50.7%	1.4 (1.2, 1.7)	55.0%	23.3%	5.8%	39.5%
Mukadam et al. (2019)	India	SR (Four-point Likert scale)	Same as above	15.3%	1.4 (1.2, 1.7)	78.0%	8.4%	2.2%	41.2%
Mukadam et al. (2019)	World	SR (Four-point Likert scale)	Same as above	17.7%	1.4 (1.2, 1.7)	27.0%	6.5%	2.6%	35.0%
Oliveira et al. (2019)	Mozambique	SR	At least moderate PA 5x p/week, 30 min p/ day OR at least vigorous PA 3x p/week, 20 min p/day	9.3%	1.82 (1.19, 2.78)	49.0%	7.1%	–	44.0% and 24.4%[b]
Oliveira et al. (2019)	Brazil	SR	Same as above	46.0%	1.82 (1.19, 2.78)	49.0%	27.4%	–	55.3% and 32.3%[b]
Oliveira et al. (2019)	Portugal	SR	Same as above	53.9%	1.82 (1.19, 2.78)	49.0%	30.7%	–	65.8% and 40.1%[b]

(Continues)

TABLE 1 (Continued)

Authors	Country	PA measure	Physical inactivity cut-off	Physical inactivity prevalence	RR for dementia	Communality	Unweighted PAF for physical inactivity	Weighted PAF for physical inactivity[b]	Overall PAF for non-modifiable RF
Feter et al. (2022)	Low and lower-middle income countries	SR (GPAQ. IPAQ)	< 150 min of MVPA per week	21.8%	1.82 (1.19, 2.78)	–	12.25%	–	–
Lee et al. (2022)	USA	SR (IPAQ)	Not doing either 75 min/week of vigorous activity or 150 min/ week of moderate activity or 150 min/week of moderate/ vigorous activity	62.8%	1.39 (1.16, 1.67)	30.0%	20.1%	–	–
Vergara et al. (2022)	Chile (45–64' years old)	SR (GPAQ)	Scored as low physical activity according to the GPAQ	33.6%	1.4 (1.2, 1.7)	59.0%	11.9%	3.3%	38.8%[b]
Vergara et al. (2022)	Chile (≥ 65 years old)	SR (GPAQ)	Scored as low physical activity according to the GPAQ	46.7%	1.4 (1.2, 1.7)	28.0%	15.6%	8.2%	56.0%[b]
Ma'u et al. (2021)	New Zealand	SR	Did not meet WHO physical activity guidelines for exercise of > 30 min a day for at least 5 days a week	53.6%	1.4 (1.2, 1.7)	44.0%	17.6%	5.2%	47.7%
Weiss (2021)	USA[a]	SR	Vigorous physical activity at least 3x p/week over the past year prior to baseline interview. SR	66.9%	1.52 (1.02, 2.25)	–	26.8%	–	–
Liu et al. (2020)	China	SR	The proportion of adults who do not exercise ≥3.5 h per week. SR	82.2%	1.39 (1.01, 1.91)	–	24.3%	–	55.0%[b]
Rolandi et al. (2020)	Italy	SR	Absence of any weekly vigorous or moderate during leisure time	47.5%	1.33 (0.90, 1.96)	-	13.3%	-	Approximately 40%
Hoffmann et al. (2022)	USA	SR	Unclear	23.9%	1.6 (1.3, 1.8)	53.0%	11.8%	–	36.9%[b]

(Continues)

TABLE 1 (Continued)

Authors	Country	PA measure	Physical inactivity cut-off	Physical inactivity prevalence	RR for dementia	Communality	Unweighted PAF for physical inactivity	Weighted PAF for physical inactivity[b]	Overall PAF for non-modifiable RF
Ashby-Mitchell et al. (2017)	Australia	SR	Not doing either 75 min/week of vigorous activity or 150 min/week of moderate activity or 150 min/week of moderate/vigorous activity SR	56.0%	1.4 (1.2, 1.7)	16.9%	17.9%	–	57.0% and 48.4%[b]
Wu et al. (2020)	China	SR	Number of conscious physical exercises per week is < 1 per week. SR	54.2%	4.1 (3.6, 4.6)	57.0%	–	–	66.8%[b]
Kotaki et al. (2019)	Japan	SR	Time spent walking < 30 min/day	33.4%	1.23 (1.04, 1.46)	–	–	19.0%	29.6%
Ashby-Mitchell et al. (2018)	Barbados	SR	Proportion of adults not meeting PA guidelines (< 150 min/week of MVPA)	49.9%	1.4 (1.2, 1.7)	11.7%	16.3%	–	–
Barnes and Yaffe (2011)	USA	SR	Proportion of adults not meeting PA guidelines (< 150 min/week of MVPA)	32.5%	1.82 (1.19, 2.78)	–	21.0%	54.1%	–
Hazar et al. (2016)	Iran	SR	Proportion of adults not meeting PA guidelines (< 150 min/week of MVPA)	35.7%	1.82 (1.19, 2.78)	–	22.0%	–	–
Ashby-Mitchell et al. (2020)	Jamaica	SR	The proportion of adults engaging in physical fitness activity 6 times or less per week	46.0%	1.39 (1.16, 1.67)	20.0%	15.21%	40.06%	34.46%
Bobrow et al. (2021)	South Africa	SR	At least moderate PA 5x p/week, 30 min p/day OR at least vigorous PA 3x p/week, 20 min p/day SR	62.0%	1.4 (1.2, 1.7)	30.0%	20.0%	–	45.0%

Abbreviations: GPAQ, global questionnaire of physical activity; IPAQ, international questionnaire of physical activity; MVPA, moderate-to-vigorous physical activity; PA, physical activity; PAF, population attributable fraction; RR, relative risk; SR, self-reported.

[a]Values reported from Hispanic women. Other ethnic (non-Hispanic black, white, and Hispanic) and sexual (men) groups showed no relationship between physical activity and incident dementia.

[b]Accounting for communality among risk factors.

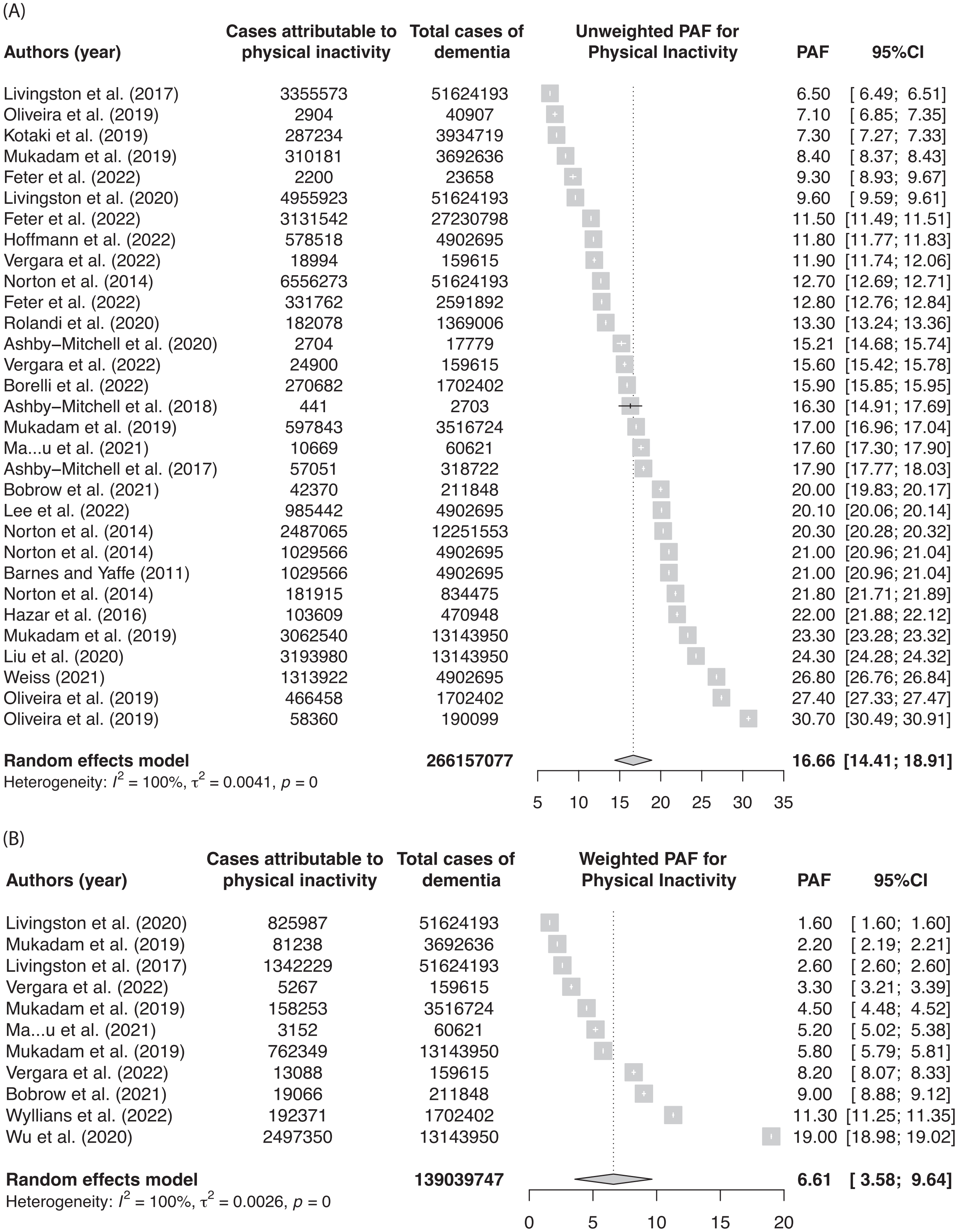

FIGURE 2 Forest plot of unweighted (A) and weighted (B) population attributable fraction (PAF) of physical inactivity to dementia. Weighted PAF represents the proportion of cases attributable to physical inactivity accounting for the communality among other modifiable risk factors. Communality was calculated and reported by each study

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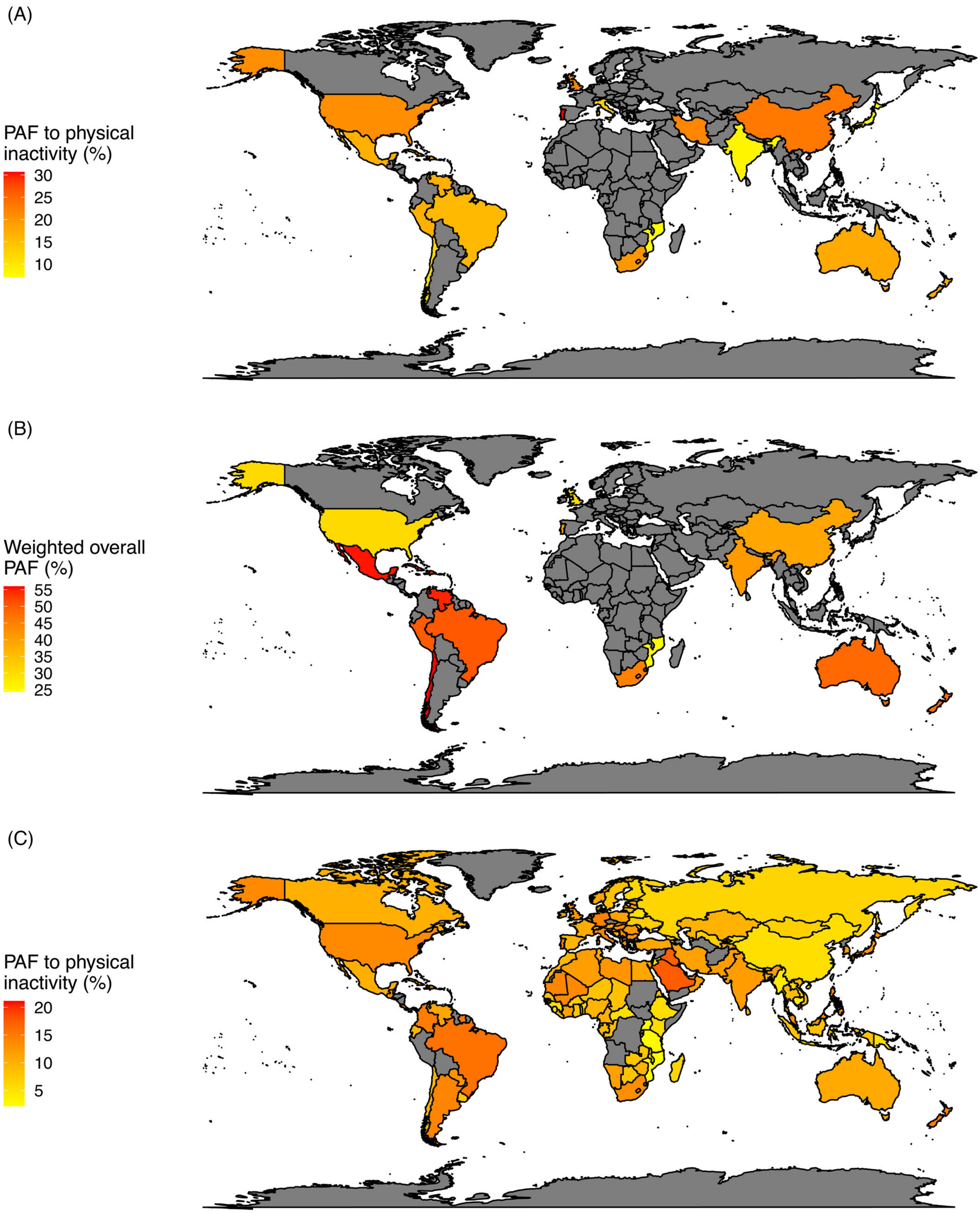

FIGURE 3 Population attributable fraction (PAF) to physical inactivity and other risk factors for dementia. (A) PAF estimated by the studies included in the present systematic review. (B) Weighted overall PAF to physical inactivity and other modifiable risk factors for dementia estimated by the included studies. (C) PAF to physical inactivity estimated using the World Health Organization's Global Health Observatory. Values are reported in percentage (%), with values indicating the proportion of cases potentially preventable

TABLE 2 Population attributable fraction to physical inactivity for dementia according to studies' subgroup analysis

	k	PAF (%)[a]	*p* value[b]	I^2 (%)[c]	τ[d]
Unweighted[e]					
Study design			0.567	100.0	
Cross-sectional	29	16.42 (14.14, 18.71)			0.06
Cohort	2	20.05 (6.82, 33.28)			0.09
Regions			0.005	100.0	
World	3	9.60 (6.09, 13.11)			0.05
Asia	6	16.13 (9.81; 22.45)			0.08
Africa	3	13.30 (5.99, 20.61)			0.07
Europe	4	21.52 (14.52, 28.53)			0.05
South and Central America	7	17.05 (13.44, 20.65)			0.05
North America	5	20.14 (15.43, 24.85)			0.05
Oceania	3	14.94 (9.41, 20.46)			0.05
Income			<0.001	100.0	
High-income	15	18.23 (15.20, 21.26)			0.07
Low and middle-income	13	16.48 (12.92, 20.04)			0.07
World	3	9.60 (6.09, 13.11)			0.05
Relative risk			<0.001	100.0	
1.82 (1.19, 2.78)	12	18.13 (13.97, 22.29)			0.07
1.39 (1.16, 1.67)	15	15.97 (13.37, 18.57)			0.05
1.52 (1.02, 2.25)	1	n/a			n/a
1.33 (0.90, 1.96)	1	n/a			n/a
1.60 (1.30, 1.80)	1	n/a			n/a
1.23 (1.04, 1.46)	1	n/a			n/a
WHO criteria for physical inactivity			0.134	100.0	
No	7	14.34 (10.33, 18.36)			0.07
Yes	21	17.94 (15.03, 20.85)			0.05
Unclear	3	13.10 (10.65, 15.55)			0.02
Weighted[f]					
Study design			n/a	100.0	
Cross-sectional	11	6.61 (3.58, 9.64)			0.05
Cohort	n/a	n/a			
Regions			<0.001		
World	2	2.10 (1.12, 3.08)			0.01
Asia	3	9.00 (0.00, 19.01)			0.09
Europe	0	n/a			n/a
South and Central America	4	6.82 (0.00, 10.39)			0.04
North America	0	n/a			n/a
Oceania	1	5.20 (5.02, 5.38)			n/a
Income			0.003		
High-income	3	5.57 (2.77, 8.36)			0.06
Low and middle-income	6	8.63 (3.82, 13.45)			0.03
World	2	2.10 (1.12, 3.08)			0.01

(Continues)

TABLE 2 (Continued)

	k	PAF (%)[a]	p value[b]	I^2 (%)[c]	τ[d]
WHO criteria for physical inactivity			0.559		
No	5	8.56 (2.66, 14.46)			0.07
Yes	4	4.60 (1.36, 7.84)			0.03
Unclear	2	5.75 (0.95, 10.55)			0.03
Communality (%)			<0.001		
29 or lower	3	7.37 (0.00, 12.36)			0.04
30–39	2	6.75 (2.34, 11.16)			0.03
40–49	1	5.20 (5.02, 5.38)			n/a
50–59	4	7.43 (−0.32, 15.17)			0.08
70–79	1	2.20 (2.19, 2.21)			n/a
Relative risk			<0.001		
4.10 (3.60, 4.60)	1	19.00 (18.98, 19.02)			n/a
1.39 (1.16, 1.67)	10	5.37 (3.37, 7.37)			0.03
1.82 (1.19, 2.78)	0	n/a			n/a
1.52 (1.02, 2.25)	0	n/a			n/a
1.33 (0.90, 1.96)	0	n/a			n/a
1.60 (1.30, 1.80)	0	n/a			n/a
1.23 (1.04, 1.46)	0	n/a			n/a
Same dataset to calculate prevalence and communality			0.002		
No	2	2.10 (1.12, 3.08)			0.01
Yes	9	7.61 (0.27, 5.15)			0.05

Abbreviations: n/a, not applicable due to insufficient observations; PAF, population attributable fraction; WHO, World Health Organization.
[a] PAF of physical inactivity to dementia, indicating the number of cases of dementia attributable to physical inactivity.
[b] *p* value for between-groups difference.
[c] I^2 measure of heterogeneity between studies expressed as percentage.
[d] tau using restricted maximum-likelihood estimator.
[e] PAF not accounting for communality.
[f] PAF accounting for communality.

($p = 0.465$) showed a low risk of publication bias. The mean (standard deviation [SD]) NOS score was 6.7 (0.6), which is suggestive of a moderate methodological quality of included studies. Representativeness of the sample was ensured in all included studies as the prevalence of physical inactivity was assessed in population-based studies. Moreover, the studies had satisfactory sample sizes. However, no studies verified the comparability between respondents and non-respondents and reported the response rate. Regarding ascertainment of exposure, physical inactivity was assessed by self-reported questionnaires in all included studies, although only five studies described the instrument used to measure physical activity levels.[11,18–20,31] All studies calculated PAF using adjusted RRs; however, some did not clearly explain the confounding factors included in the model. Finally, studies clearly defined the formula and the source of its components. More detailed information about the quality assessment of studies included in this meta-analysis can be seen in Table S6.

3.5 | Global impact of physical inactivity on the prevalence of dementia

Under a "best" estimate scenario, we illustrated the proportion of cases of dementia attributable to physical inactivity in all countries with the prevalence of physical inactivity available at the WHO's Global Health Observatory ($n = 162$) (Figure 3C). The Arabian Peninsula and South America were regions with the highest PAFs, corroborating the findings of our systematic review. The highest PAF was observed in Kuwait (21.1%), followed by Saudi Arabia (17.5%), Iraq (17.2%), and Brazil (15.8%). The lowest PAF was in Uganda (2.2%), followed by Mozambique (2.2%), Lesotho (2.4%), and Tanzania (2.5%).

4 | DISCUSSION

One new case of dementia is discovered every three seconds worldwide.[2] Based on our more conservative findings, physical activity

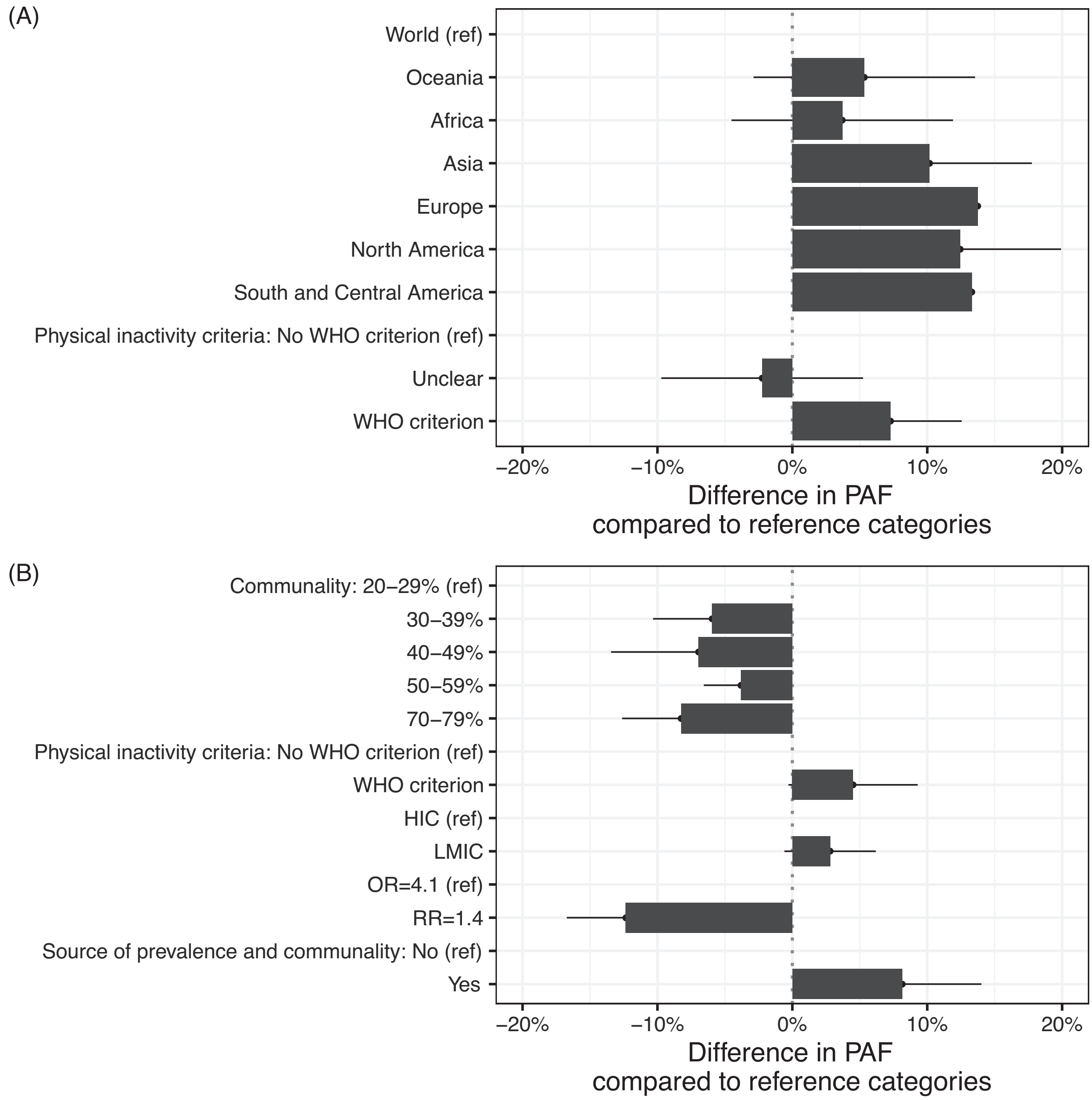

FIGURE 4 Results from multivariable meta-regression analyses for studies' characteristics to predict the unweighted (A) and weighted (B) PAF to physical inactivity for dementia. Results are reported as difference in the proportion of cases of dementia attributable to physical inactivity compared to the reference category. Unclear refers to studies in which it was not possible to identify how the authors defined physical inactivity. Lines in each bar represent 95% confidence interval. HIC, high-income countries; LMIC, low- and middle-income countries; OR, odds ratio; ref, reference category; PAF, population attributable fraction; RR, relative risk; WHO, World Health Organization

can prevent one in every fifteen cases of dementia, which represents one case every 45 s. Studies using WHO criteria for physical inactivity obtained higher PAFs than those using other criteria. Also, studies in which communality and physical inactivity prevalence were calculated using the same dataset showed higher PAF than those using different sources. The cost of dementia will increase by US$1.5 trillion from 2020 to 2030, reaching US$2.8 trillion worldwide.[32] Thus, we estimated that the economic burden of physical inactivity would be US$99 billion in direct and indirect costs of new cases of dementia.[32] Also, the incidence of dementia is increasing rapidly in less developed regions, which will house three-quarters of all cases of dementia by 2050.[2] Physical activity can be a potential alternative to reduce the incidence of dementia, especially in countries where fragile healthcare systems might collapse due to the burden of dementia soon.

Previous studies have demonstrated the impact of physical inactivity on several chronic conditions. In 2012, Lee et al.[7] revealed that one in ten deaths in 2008 was attributable to physical inactivity. With regard to dementia specifically, Livingston et al.[5] showed that 40% of all cases of dementia are attributable to modifiable risk factors, including physical inactivity.[33–35] PAF can be very useful for decision-makers and public health agencies for promoting physical activity at the populational level. Thus, it is essential to obtain accurate estimates of the PAF.

Previous systematic reviews and meta-analyses have confirmed the association between physical inactivity and the risk of all-cause dementia.[36–39] However, some gaps remain, especially on the weight of each modifiable risk factor on the risk of dementia. Our findings indicate that up to one in six cases of dementia worldwide are attributable to physical inactivity; however, after adjusting for communality among risk factors, the value lowered to one in 15. We understand the importance of communality as a strategy to account for overlapping risk factors. However, the multifactorial feature of dementia impairs understanding the influence of individual risk factors on the risk for the disease. For example, it remains unclear if multiple risk factors have an addictive or synergistic effect. Also, physical inactivity is associated with an increased risk of several risk factors for dementia, such as obesity, hypertension, diabetes, and depression. Thus, a completely independent effect seems unreasonable, considering that those risk factors are in the causal pathway between physical inactivity and dementia. An alternative approach might be joint association analyses to precisely calculate the weight of each risk factor on the risk of dementia. For instance, physical activity can attenuate or even eliminate the risk of other risk factors such as sedentary behavior,[40] sleep,[41] and obesity[42] on all-cause mortality. Similarly, physical activity mitigated the impact of important risk factors, including aging and cardiovascular diseases, on the risk of incident dementia.[43,44] Although most of the included studies had cross-sectional designs, population-based cohort studies have been conducted using extensive cognitive and clinical batteries to examine the presence of dementia.[45–48] Future studies such as harmonized individual participants' data meta-analyses may provide valuable evidence on the weight of different risk factors on all-cause dementia.

Moreover, most studies used similar RR (i.e., 1.40 vs. 1.82) estimated in a previous meta-analysis published in 2009 with 163,797 participants with no dementia at baseline.[49] The meta-analysis calculated the RR of physical inactivity to dementia (RR = 1.4) and Alzheimer's disease (RR = 1.8). However, some PAFs to all-cause dementia were calculated using the RR for Alzheimer's disease. Also, several meta-analyses on this matter have been published recently.[36–39] For example, Iso-Markku et al.[39] analyzed data of 257,983 participants from 58 studies. The study found a more conservative and precise RR (1.3; 95% CI: 1.2, 1.3). In addition, these pooled RRs were estimated using prospective cohort studies conducted primarily in high-income countries, as studies in less developed countries are scanty. Longitudinal studies with older adults in China[50] and Cuba[51] demonstrated that physical inactivity was associated with a higher risk of dementia (RR = 1.5 and RR = 2.2, respectively). Furthermore, the RR and prevalence of physical inactivity have been estimated using different data collection instruments to calculate the PAF. Studies included in previous systematic reviews to calculate the RR of physical inactivity for dementia defined physical inactivity using various criteria. For example, some studies used the WHO criteria (< 150 min of moderate-to-vigorous physical activity per week), while others compared the risk of dementia between the most and least active quintiles.[39] Longitudinal studies in a large, multiethnic, and cognitively diverse population are required to improve understanding of the impact of physical inactivity in regions facing a rapidly increasing incidence of dementia.

The high agreement of the PAF formula used among included studies may not indicate reliability. Levin's formula uses unadjusted RR and the prevalence of physical inactivity in the source population. However, most meta-analyses reported RR of dementia comparing inactive with active people adjusted for other risk factors (e.g., education, diabetes). In this case, a second formula would be more appropriate, as shown in Supplementary Panel 1, where P_{cases} is the proportion of inactive people among cases, and RR_{adj} is the RR adjusted for confounding factors. The use of adjusted RR in the original Levin's formula is likely to underestimate the PAF rather than overestimate it.[28] In addition, the risk factors included in the principal component analysis to derive communality were, in most cases, the same used to derive the adjusted RR of dementia between active and inactive adults. For example, Kotaki et al.[52] showed that the PAF of physical inactivity for all-cause dementia was 17.3% using a crude RR. However, the fraction decreased to 9.3% when RR was adjusted for age and sex and then to 7.3% when including diabetes, hypertension, body mass index, psychological disorders, and educational level in the model. All studies included in this review calculated PAF using RR adjusted at least for age, sex, education, diabetes, and hypertension. Thus, the RRs represent the risk of dementia associated with physical inactivity independently of other modifiable risk factors. The pooled PAF of studies using only the adjusted RR and the prevalence of physical inactivity was 16.7%. However, the weighted PAF (6.6%), calculated by accounting for communality across other risk factors (e.g., low education, diabetes, and hypertension) was 153% lower than the unweighted PAF. Moreover, no study has investigated whether the downgrading of the attributable fraction to physical inactivity is associated with the "double-adjustment" of other risk factors to generate communality. Future investigations of statistical approaches are strongly recommended to provide policymakers and health professionals with precise and consistent findings.

Our results suggested that the definition of physical inactivity is associated with the PAF. Over the years, different definitions have been used primarily due to the lack of a more quantitative (minutes per week) measure of physical activity in some studies. The 2020 WHO guidelines for physical activity and sedentary behavior detail the optimal amount of physical activity associated with several health benefits for different age and population groups.[10] The guideline recommends 150 to 300 min of moderate-intensity physical activity or 75 to 150 min of vigorous-intensity physical activity throughout the week, or the equivalent combination of moderate and vigorous activities.[10] Since then, surveillance surveys worldwide have adopted the WHO guidelines to improve comparability across countries. Also, country-level public health policies require accurate indicators to design efficient programs to promote physical activity. Thus, underestimation and overestimation of the physical inactivity prevalence will impair public health messages on the most efficient strategies to reduce diseases. For example, four studies included in this review estimated the global impact of physical inactivity on dementia. The authors considered the worldwide prevalence of physical inactivity was 18% from 2011 to 2020. However, more recent evidence showed that the global prevalence of physical inactivity was 27.5% (95% CI: 25.0%, 32.2%) in 2016, which was 55.4% higher than the previous estimate.[53]

Moreover, our findings support the potential benefit of promoting physical activity, especially in less developed countries.[5,8,11] The number of people living with dementia from 2019 to 2050 will be 113% higher in low- and middle-income countries than in high-income countries.[4] Population growth and aging, increased prevalence of cardiovascular diseases, and other risk factors for dementia explained the higher incidence in these regions.[4] Previous successful experiences in high-income countries evidenced the importance of promoting a healthy lifestyle, including physical activity, to improve cardiometabolic health, ultimately leading to reduced incidence of dementia.[54] Low- and middle-income countries have a wider window of opportunity to reduce the burden of dementia, considering that more than half of the cases are attributable to modifiable risk factors.[11] However, the message must be concise, consistent, and clear. Constant promotion of physical activity across the lifespan is critical to preserve cognitive function and reduce the risk of dementia in older ages.

Large, population-based, prospective studies have been performed worldwide. However, most are still conducted in developed countries. Initiatives, including the Global Alzheimer's Association Interactive Network (GAAIN) and the Gateway of Global Aging, are critical to providing evidence of the interaction between the incidence of dementia and its risk factors through harmonized datasets. The WHO's *Global Status Report on Physical Activity 2022* reveals the slow progress since 2017 in public health policies to monitor, promote, and evaluate physical activity programs at the national level. PAF provides policy makers with valid quantitative estimates of the potential effect of interventions to reduce or eradicate the risk factor. The WHO's *Global Action Plan on Physical Activity* provides a policy framework for achieving a 15% relative reduction in the prevalence of physical inactivity by 2030.[55] Similarly, the *Global Action Plan on the Public Health Response to Dementia 2017-2025*, created by the WHO in 2017, aimed to reduce the prevalence of physical inactivity by 10% in 2025.[3] However, these targets are unlikely to be reached as the prevalence of physical inactivity has been unchanged between 2001 and 2016.[56] Considering the high prevalence of physical inactivity in older adults and its impact on health, policies for "age-friendly" cities, programs, and services tailored for older adults are suggested.[57] However, previous evidence has stressed the difficulty of moving from recommendations to implemented population-level programs and strategies.[57] Therefore, the accurate estimation of impact measures, including the PAF, is crucial for involving people, communities, and policymakers in corroborating the protective effect of physical activity in reducing the risk of noncommunicable chronic conditions such as dementia.

The present study has limitations that need to be acknowledged. First, the low number of studies in some regions (e.g., Africa and Oceania) limited our estimation of PAF in less developed countries. Although two-thirds of the cases of dementia are housed in low- and middle-income countries, the data from these regions are scarce. Such limitation impairs our ability to identify the most cost-effective strategy to control the increasing incidence of dementia. Second, we only calculated the PAF for all-cause dementia. However, the number of studies investigating the PAF for physical inactivity to specific types of dementia, such as vascular dementia and frontotemporal dementia, is scanty. Third, we found only two prospective cohort studies investigating the impact of physical inactivity on dementia incidence. Most studies calculate PAF using RR of all-cause dementia from a previous meta-analysis and the study-specific prevalence of risk factors. In future studies, PAF of physical inactivity may be calculated from population-based studies with longitudinal data acquisition to clarify the impact of physical inactivity on dementia. We cannot rule out reverse causality, which has been shown to influence the association between physical activity and the risk of dementia.[58] Also, a more recent formula was suggested to calculate PAF accounting for communality, providing a more accurate estimation of the burden of disease that is attributable to several risk factors.[59] Finally, our findings are based on moderate-quality evidence according to the NOS while Egger's tests and funnel plots did not suggest a potential effect of publication bias in our findings. However, some results lost significance after permutation tests, especially on weighted PAFs. More studies with more diverse populations, including people with different cognitive reserves and ethnic backgrounds, are required to estimate the number of potentially preventable cases of dementia correctly. Future cross-sectional studies investigating the impact of physical inactivity on dementia must primarily focus on improved reporting and statistical approaches to provide robust evidence about the association between these two epidemics that broadly impact global health.

Our findings corroborate the literature suggesting a significant impact of physical inactivity on dementia. However, some methodological characteristics must be considered for future research. First, standardized physical inactivity definitions are recommended to provide accurate and comparable estimates. Second, prospective cohort studies are warranted as this is the recommended study design to calculate the PAF. However, we only found two longitudinal studies that meet the inclusion criteria. Considering that the low physical activity level in older ages may be attributable to prodromal dementia, cohort studies with long follow-up periods (≥10 years) are recommended to investigate the association between physical inactivity and the risk of dementia.[58] Finally, accurate PAF of physical inactivity to dementia is required to support physical activity interventions and policies, particularly those targeting older adults.

5 | CONCLUSION

In conclusion, we conservatively estimated that one in 15 cases of dementia can be attributable to physical inactivity. Physical activity has been confirmed as a non-pharmacological, low-cost, and adverse-event-free approach to reducing the risk of all-cause dementia. We must support all efforts to reduce physical inactivity as an efficient strategy to reduce the burden of dementia.

AUTHOR CONTRIBUTIONS

Natan Feter and Jayne S. Leite contributed to the conception or design of the work. Natan Feter drafted the manuscript. Natan Feter, Jayne S. Leite, Luísa Silveira da Silva, Júlia Cassuriaga, Danilo de Paula, Gabriela Wünsch Lopes, Pedro Rodrigues Curi Hallal, I-Min Lee, and Airton José Rombaldi contributed to the acquisition, analysis, or interpretation of data for the work. Pedro Rodrigues Curi Hallal, I-Min Lee, and Airton José Rombaldi critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy. Natan Feter accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish

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CONFLICT OF INTEREST STATEMENT

The authors declare there are no conflicts of interest. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

The dataset and scripts used to perform this study are available at https://osf.io/wt3ja/?view_only=231ff60bc3854b0c9afb6307a02e0a90.

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REFERENCES

1. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study2019. *The Lancet*. 2020;396:1204-1222. Elsevier.
2. Patterson C. World Alzheimer Report 2018—The state of the art of dementia research: new frontiers. *Alzheimer's Dis Int (ADI)*. 2018. London, UK. Epub.
3. World Health Organization (WHO). Global action plan on the public health response to dementia 2017-2025. *World Health Organization*. Epub 2017.
4. Collaborators GBD 2019 DF. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Pub Health*. Elsevier; Epub 2022.
5. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*. 2020;396:413-446. Elsevier.
6. Mansournia MA, Altman DG. Population attributable fraction. *BMJ*. 2018:360. British Medical Journal Publishing Group.
7. Lee IM, Shiroma EJ, Lobelo F, et al. *Effect of Physical Inactivity on Major Non-Communicable Diseases Worldwide: An Analysis of Burden of Disease and Life Expectancy*. 2012:219-229. Accessed at. https://www.ncbi.nlm.nih.gov/pubmed/22818936. Lancet [online serial]. Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School. ilee@rics.bwh.harvard.edu.
8. Oliveira D, Jun Otuyama L, Mabunda D, et al. Reducing the number of people with dementia through primary prevention in Mozambique, Brazil, and Portugal: an analysis of population-based data. *J Alzheimer's Dis*. 2019;70:S283-S291. IOS Press.
9. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol Lancet Publishing Group*. 2014;13:788-794.
10. WHO, WHO guidelines on physical activity and sedentary behaviour. World Health Organization; Epub 2020.
11. Mukadam N, Sommerlad A, Huntley J, Livingston G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *Lancet Glob Health*. 2019;7:e596-e603. Elsevier Ltd.
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ Publishing Group*. 2021:372. Accessed November 28, 2022. Accessed at. https://www.bmj.com/content/372/bmj.n71
13. Herzog R, Alvarez-Pasquin MJ, Diaz C, del Barrio JL, Estrada JM, Gil A. Newcastle-Ottawa Scale adapted for cross-sectional studies. *BMC Public Health*. 2013;13:154.
14. Schwarzer G, General Package for Meta-Analysis. 2016.
15. (WHO) WHO. Global health observatory. *Geneva*. 2019.
16. Weiss J. Contribution of socioeconomic, lifestyle, and medical risk factors to disparities in dementia and mortality. *SSM Popul Health*. 2021:16. Elsevier Ltd.
17. Rolandi E, Zaccaria D, Vaccaro R, et al. Estimating the potential for dementia prevention through modifiable risk factors elimination in the real-world setting: a population-based study. *Alzheimers Res Ther*. 2020:12. BioMed Central Ltd.
18. Borelli WV, Leotti VB, Strelow MZ, Chaves ML, Castilhos RM. Preventable risk factors of dementia: Population attributable fractions in a Brazilian population-based study. *Lancet Reg Health Am*. 2022;11:100256.
19. Feter N, Leite JS, Cassuriaga J, et al. *Are gender differences in physical inactivity associated with the burden of dementia in low- and lower-middle income countries?* Glob Public Health. 2022;17(5):727-737.
20. Vergara RC, Zitko P, Slachevsky A, San Martin C, Delgado C. Population attributable fraction of modifiable risk factors for dementia in Chile. *Alzheimer's Dement Diag Assess Dis Mon*. 2022:14. Wiley.
21. Ashby-Mitchell K, Burns R, Anstey KJ. The proportion of dementia attributable to common modifiable lifestyle factors in Barbados. *Revista Panamericana de Salud Publica*. 2018;42:e17. SciELO Public Health.
22. Ashby-Mitchell K, Willie-Tyndale D, Eldemire-Shearer D. Proportion of dementia explained by five key factors in Jamaica. *J Alzheimers Dis*. 2020;78:603-609.
23. Hoffmann CM, Nianogo RA, Yaffe K, Rosenwohl-Mack A, Carrasco A, Barnes DE. Importance of accounting for regional differences in modifiable risk factors for Alzheimer's disease and related dementias: The case for tailored interventions. *J Alzheimer's Dis*. 2022(Preprint): 1-8.
24. Hazar N, Seddigh L, Rampisheh Z, Nojomi M. Population attributable fraction of modifiable risk factors for Alzheimer disease: A systematic review of systematic reviews. *Iran J Neurol*. 2016;15(3):164.
25. Bobrow K, Hoang T, Barnes DE, Gardner RC, Allen IE, Yaffe K. The effect of sex and wealth on population attributable risk factors for dementia in south Africa. *Front Neurol*. 2021;12:766705.
26. Liu Y, Zhang S, Tomata Y, Nurrika D, Sugawara Y, Tsuji I. The impact of risk factors for dementia in China. *Age Ageing*. 2020;49:850-855. Oxford University Press.
27. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *The Lancet*. 2017;390:2673-2734. Elsevier.

28. Barnes D, Yaffe K. The projected impact of risk factor reduction on Alzheimer's disease prevalence. *Alzheimers Dement*. 2011;7:S511-S511. Elsevier.
29. Ashby-Mitchell K, Burns R, Shaw J, Anstey KJ. Proportion of dementia in Australia explained by common modifiable risk factors. *Alzheimers Res Ther*. 2017:9. BioMed Central Ltd.
30. Ma'u E, Cullum S, Cheung G, Livingston PG, Mukadam N. Differences in the potential for dementia prevention between major ethnic groups within one country: a cross sectional analysis of population attributable fraction of potentially modifiable risk factors in New Zealand. *Lancet Reg Health West Pac*. 2021:13. Elsevier Ltd.
31. Lee M, Whitsel E, Avery C, et al. Variation in population attributable fraction of dementia associated with potentially modifiable risk factors by race and ethnicity in the US. *JAMA Netw Open*. 2022;5:E2219672. American Medical Association.
32. Gauthier S, Rosa-Neto P, Morais JA, Webster C. World Alzheimer Report 2021: journey through the diagnosis of dementia. *Alzheimer's Dis Int*. Epub. 2021.
33. Inactivity "killing as many as smoking" - BBC News [online]. Accessed at: Accessed November 10, 2022. https://www.bbc.com/news/uk-wales-politics-18876880
34. Physical inactivity kills 5.3 million a year globally | CBC News [online]. Accessed at: Accessed November 10, 2022. https://www.cbc.ca/news/health/physical-inactivity-kills-5-3-million-a-year-globally-1.1249364
35. Eliminating These 12 Risk Factors Could Cut Global Dementia Rates by 40% | Technology Networks [online]. Accessed at: Accessed November 21, 2022. https://www.technologynetworks.com/neuroscience/news/eliminating-these-12-risk-factors-could-cut-global-dementia-rates-by-40-338098
36. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?: a systematic review and meta-analysis of longitudinal studies. *BMC Public Health*. 2014;14:510.
37. Guure CB, Ibrahim NA, Adam MB, Said SM. Impact of physical activity on cognitive decline, dementia, and its subtypes: meta-analysis of prospective studies. *Biomed Res Int*. 2017;2017:9016924.
38. Xu W, Wang HF, Wan Y, Tan C-C, Yu J-T, Tan L. Leisure time physical activity and dementia risk: a dose-response meta-analysis of prospective studies. *BMJ Open*. 2017;7:e014706-e014706.
39. Iso-Markku P, Kujala UM, Knittle K, Polet J, Vuoksimaa E, Waller K. Physical activity as a protective factor for dementia and Alzheimer's disease: systematic review, meta-analysis and quality assessment of cohort and case–control studies. *Br J Sports Med*. 2022. Accessed at. http://bjsm.bmj.com/content/early/2022/03/14/bjsports-2021-104981.abstract. [online serial]. Epub. Mar.:bjsports-2021-104981.
40. Ekelund U, Brown WJ, Steene-Johannessen J, et al. Do the associations of sedentary behaviour with cardiovascular disease mortality and cancer mortality differ by physical activity level? A systematic review and harmonised meta-analysis of data from 850 060 participants. *Br J Sports Med*. 2019;53:886-894. Accessed at. http://bjsm.bmj.com/content/53/14/886.abstract. [online serial].
41. Chen L-J, Hamer M, Lai Y-J, Huang B-H, Ku P-W, Stamatakis E. Can physical activity eliminate the mortality risk associated with poor sleep? A 15-year follow-up of 341,248 MJ Cohort participants. *J Sport Health Sci*. 2022;11:596-604. Accessed at. https://www.sciencedirect.com/science/article/pii/S2095254621000260. [online serial].
42. Sanchez-Lastra MA, Ding D, Dalene K-E, Ekelund U, Tarp J. Physical activity and mortality across levels of adiposity: a prospective cohort study from the UK biobank. *Mayo Clin Proc*. 2021;96:105-119. Accessed at. https://www.sciencedirect.com/science/article/pii/S0025619620307564. [online serial].
43. Feter N, Mielke GI, Cunha L, Leite JS, Dumith SC, Rombaldi AJ. Can physical activity attenuate the impact of cardiovascular risk factors in the incidence of dementia? Findings from a population-based cohort study. *Psychiatry Res*. 2022;317:114865.
44. Feter N, Dumith SC, Smith EC, et al. Physical activity attenuates the risk for dementia associated with aging in older adults with mild cognitive impairment. Findings from a population-based cohort study. *J Psychiatr Res*. 2021;141:1-8.
45. Minicuci N, Naidoo N, Chatterji S, Kowal P. Data Resource Profile: cross-national and cross-study sociodemographic and health-related harmonized domains from SAGE plus ELSA, HRS and SHARE (SAGE+, Wave 1). *Int J Epidemiol*. 2016;45:1403. Oxford University Press.
46. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English longitudinal study of ageing. *Int J Epidemiol*. 2013;42:1640-1648. Oxford University Press.
47. Langa KM, Ryan LH, McCammon RJ, et al. The health and retirement study harmonized cognitive assessment protocol project: study design and methods. neuroepidemiology. *Karger Publishers*. 2020;54:64-74. Accessed at. Accessed November 12, 2022. https://www.karger.com/Article/FullText/503004. [online serial].
48. Meng Q, Wang H, Strauss J, et al. Validation of neuropsychological tests for the China Health and Retirement Longitudinal Study Harmonized Cognitive Assessment Protocol. *Int Psychogeriatr*. 2019;31:1709-1719. Accessed at: Accessed November 12, 2022. https://www.cambridge.org/core/journals/international-psychogeriatrics/article/abs/validation-of-neuropsychological-tests-for-the-china-health-and-retirement-longitudinal-study-harmonized-cognitive-assessment-protocol/6C2FC5C7A7CE28FF4F6BF20A30C9DE04. [online serial]. Cambridge University Press.
49. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychol Med*. 2009;39:3-11.
50. Wu W, Ding D, Zhao Q, et al. Medium-to-high late-life physical activity is associated with lower risk of incident dementia: the shanghai aging study. *J Alzheimer's Dis*. 2020;73:751-758. IOS Press.
51. Peeters G, Almirall Sanchez A, Llibre Guerra J, et al. Risk factors for incident dementia among older cubans. front public health. *Front Media SA*. 2020;8:481.
52. Kotaki Y, Tomata Y, Tanji F, Zhang S, Sugawara Y, Tsuji I. Joint impact of seven risk factors on incident dementia in elderly Japanese: the Ohsaki Cohort 2006. *Study J Neurol*. 2019;266:1222-1229.
53. Guthold R, Ono T, Strong KL, Chatterji S, Morabia A. Worldwide variability in physical inactivity: a 51-country survey. *Am J Prev Med*. 2008;34:486-494. Elsevier.
54. Ahmadi-Abhari S, Guzman-Castillo M, Bandosz P, et al. Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. *BMJ Publishing Group*. 2017:358.
55. Global Action Plan on Physical Activity 2018-2030: More Active People for a … - World Health Organization - Google Books [online]. 2023. Accessed April 21. Accessed at: https://books.google.com.br/books?hl=en&lr=&id=RnOyDwAAQBAJ&oi=fnd&pg=PA48&dq=World+Health+Organization.+Global+action+plan+on+physical+activity+2018%E2%80%932030:+more+active+people+for+a+healthier+world.+Geneva+2018.&ots=GPivOhIFYl&sig=CMExs257EVn9ztlsI-PxPp_L9Yc&redir_esc=y#v=onepage&q=World%20Health%20Organization.%20Global%20action%20plan%20on%20physical%20activity%202018%E2%80%932030%3A%20more%20active%20people%20for%20a%20healthier%20world.%20Geneva%202018.&f=false
56. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. *Lancet Glob Health*. 2018;6:e1077-e1086. Elsevier.
57. Tiedemann A, Sherrington C, Bauman A, Ding D, Supporting physical activity in an ageing world: a call for action. Lancet Reg Health West Pac [online serial]. Elsevier Ltd; 2022;0:100546. Accessed

at: Accessed April 21, 2023. http://www.thelancet.com/article/S2666606522001614/fulltext
58. Kivimäki M, Singh-Manoux A, Pentti J, et al. Physical inactivity, cardiometabolic disease, and risk of dementia: an individual-participant meta-analysis. *BMJ*. 2019:365. Accessed at. https://www.embase.com/search/results?subaction=viewrecord&id=L627290365&from=exportU2-L627290365. (Online) [online serial]. M. Kivimäki. Department of Epidemiology and Public Health, University College London, London, United Kingdom.
59. Niedhammer I, Chastang JF. Overall fraction of disease attributable to multiple dependent risk factors: a new formula. *Lancet Neurol*. 2021;20:979-980. Accessed at. Accessed April 22, 2023. http://www.thelancet.com/article/S1474442221003665/fulltext. [online serial]. Elsevier Ltd.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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