Temporal changes in personal activity intelligence and the risk of incident dementia and dementia related mortality: A prospective cohort study (HUNT)

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Summary

Background The Personal Activity Intelligence (PAI) translates heart rate during daily activity into a weekly score. Obtaining a weekly PAI score ≥100 is associated with reduced risk of premature morbidity and mortality from cardiovascular diseases. Here, we determined whether changes in PAI score are associated with changes in risk of incident dementia and dementia-related mortality.

Methods We conducted a prospective cohort study of 29,826 healthy individuals. Using data from the Trøndelag Health-Study (HUNT), PAI was estimated 10 years apart (HUNT1 1984−86 and HUNT2 1995−97). Adjusted hazard-ratios (aHR) and 95%-confidence intervals (CI) for incidence of and death from dementia were related to changes in PAI using Cox regression analyses.

Findings During a median follow-up time of 24.5 years (interquartile range [IQR]: 24.1-25.0) for dementia incidence and 23.6 years (IQR: 20.8−24.2) for dementia-related mortality, there were 1998 incident cases and 1033 dementia-related deaths. Individuals who increased their PAI score over time or maintained a high PAI score at both assessments had reduced risk of dementia incidence and dementia-related mortality. Compared with persistently inactive individuals (0 weekly PAI) at both time points, the aHRs for those with a PAI score ≥100 at both occasions were 0.75 (95% CI: 0.58−0.97) for incident dementia, and 0.62 (95% CI: 0.43−0.91) for dementia-related mortality. Using PAI score <100 at both assessments as the reference cohort, those who increased from <100 at HUNT1 to ≥100 at HUNT2 had aHR of 0.83 (95% CI: 0.72−0.96) for incident dementia, and gained 2.8 (95% CI: 1.3−4.2, P<0.0001) dementia-free years. For dementia-related mortality, the corresponding aHR was 0.74 (95% CI: 0.59−0.92) and years of life gained were 2.4 (95% CI: 1.0−3.8, P=0.001).

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Interpretation Maintaining a high weekly PAI score and increases in PAI scores over time were associated with a reduced risk of incident dementia and dementia-related mortality. Our findings extend the scientific evidence regarding the protective role of PA for dementia prevention, and suggest that PAI may be a valuable tool in guiding research-based PA recommendations.

Research in context

Evidence before this study

Personal activity intelligence (PAI) is a personalized physical activity (PA) metric that quantifies the amount of weekly PA needed to reduce the risk of premature morbidity and mortality from non-communicable diseases, regardless of whether contemporary recommendations for PA are met or not. We searched PubMed for all studies up until the 15th of June 2022, using the search terms: "PA", "exercise", "PAI" and "dementia-incidence", "dementia-related mortality". No studies had investigated the association between PAI and risk of dementia.

Added value of this study

Maintaining a weekly PAI score ≥ 100 was associated with significant reductions in risk of dementia regardless of whether contemporary recommendations for PA were met or not. This suggests PAI to be a more precise estimate to guide how much PA is needed to reduce dementia risk compared to current PA recommendations. Our results also suggest that small, concrete, and quantifiable increases in PA, which are attainable for most people worldwide, may be adequate to substantially reduce dementia risk. This is potentially a very impactful public health message and may be particularly useful in transitioning those who are habitually sedentary to some level of PA, conferring significant health benefits.

Implications of all the available evidence

Lack of time and inability to self-manage are often cited as main barriers to performing adequate PA. The PAI metric, which is incorporated into a heart rate-measuring wearable, provides readily available and quantifiable feedback on an individual's PA level, which in turn may serve both as a motivator of PA for the individual and as an important digital tool in health management among clinicians to enhance the potential for dementia prevention in their patients. Future research on the role of the PAI metric for disease risk modification is warranted in different races and ethnicities, as the increasing dementia prevalence poses an increasing threat to global public health.

Introduction

The number of people living with dementia is rising exponentially and projected to reach 150 million by 2050.[1] The ripple effect extends from the individual and their family to society, and with global costs estimated at an annual US $1 trillion,[1] preventing dementia has emerged as a major priority for public health.[2]

A growing body of evidence supports physical inactivity as a modifiable risk factor for dementia.[3-5] Moreover, systematic reviews and meta-analyses of longitudinal observational studies provide convincing evidence for the protective effects of regular physical activity (PA) in combatting dementia.[6,7] However, data regarding the volume or dosage of PA needed for a beneficial effect is limited.[8]

Accumulating evidence suggests that improving or maintaining a high cardiorespiratory fitness (CRF) is associated with protection against dementia.[9-12] Notably, the World Health Organization (WHO) states that aerobic exercise plays a key role in the magnitude of risk reduction.[13]

Personal activity intelligence (PAI), a personalized PA metric, has been developed to help quantify the amount of weekly PA needed to reduce the risk of premature morbidity and mortality from non-communicable diseases.[14,15] The PAI algorithm considers an individual's sex, age, resting and maximal heart rate and heart rate fluctuations over time, which provides an approximation of the relative exercise intensity and associated energy expenditure, and translates it into an easily understandable score which reflects the individual's cumulative weekly PA (0 PAI = inactive, 100 PAI = optimally active). A PAI score of 100 per week can be obtained by performing any type of PA volume and intensity if heart rate is elevated above a certain threshold often enough.[15]

Healthy individuals who regularly attain a weekly PAI score ≥100 have high age- and sex-specific CRF levels, more favourable cardiovascular risk factor profiles[14,16,17] and a lower risk of all-cause and cardiovascular mortality when compared with their inactive counterparts, independent of whether contemporary PA recommendations are met or not.[18,19] Regularly obtaining

a weekly PAI score ≥100 has also been associated with a reduced risk of premature mortality in patients with established cardiovascular disease (CVD)[20] when compared with their inactive counterparts.

Here, we test the hypothesis that the volume of PA, as assessed by the PAI score over time, is associated with the risk of incident dementia and dementia-related mortality in healthy women and men at baseline.

Methods

Study population

The Trøndelag Health Study (HUNT, previously Nord-Trøndelag Health Study) is a population-based health study conducted in the former Nord-Trøndelag county (now Trøndelag county) located in central Norway and includes 4 surveys (HUNT1: 1984−1986, HUNT2: 1995−1997, HUNT3: 2006−2008, and HUNT4: 2017 −2019) in which individuals are followed up longitudinally, and through several comprehensive national health registries. All adults aged 20 years and older were invited to participate in the surveys where they filled out questionnaires pertaining to health status and lifestyle, and underwent health measurements. Detailed accounts of the HUNT surveys have been previously described.[21] In this study, we used data from HUNT1 (recruitment: Jan 5, 1984 to Feb 15, 1986) and HUNT2 (recruitment: Aug 15, 1995 to June 18, 1997). Of the 33,905 individuals who participated in both HUNT1 and HUNT2 and had PA data available, individuals with a self-reported history of myocardial infarction or stroke (n=1965) and those with missing data on various potential confounders (n=2114) were excluded. A total of 29,826 individuals (15,577 women and 14,249 men) were included in our current analyses (Figure 1). All individuals provided written informed consent before enrolment. The study was approved by the Data Inspectorate and the Regional Committee on Medical and Health Research Ethics of Norway (2020/REK Midt 68184). The study sponsor was Äivind Rognmo, Head of Department of Circulation and Medical Imaging at the Norwegian University of Science and Technology, Trondheim, Norway.

Personal Activity Intelligence (PAI)

PAI scores for each participant at both HUNT waves were estimated using the responses to PA questions, with specific reference to duration, frequency, and relative intensity.[14,15,19,20] The metric includes a non-linear scaling of exercise intensity, as fewer exercise sessions of higher intensities are associated with similar or greater health benefits compared with frequent sessions at lower intensities. Thus, a unique feature of PAI is that it gives more credit for vigorous exercise than mild-to-moderate PA. Finally, it is easier to earn the first 50

PAI vs the next 50 PAI because of an exercise-induced lowering of resting and submaximal heart rates, and the fact that moving from an inactive state to an active one is associated with a relatively larger reduction in mortality risk compared with moving from a relatively active to a highly active state.[15] A more detailed description of the PAI algorithm is provided in the online supplementary material.

End points and follow-up

The HUNT data were linked to a local Hospital Dementia register and the patient administration system in Nord-Trøndelag Hospital Trust for dementia incidence. The retrospective Hospital Dementia register also includes data of the Health and Memory Study[22] on dementia diagnoses collected between 1995 and 2010 by the Nord-Trøndelag Hospital Trust. Specialists within geriatric and psychogeriatric medicine diagnosed each case according to national and international guidelines.[22] Data on cause and date of death were requested from the Norwegian Cause of Death Registry. For this study, dementia-related deaths were identified as either the immediate cause of death, the underlying cause of death, or the contributing cause of death, using the International Classification of Diseases, 9th revision: 290·0−290·9, 294·2, 331, or International Classification of Diseases, 10th revision: F00−F03 and G30−G31·8. The data on dementia incidence and mortality were accurately matched to each participant through their 11-digit personal identification number. The registration in the population registries is mandatory in Norway, therefore, our study had a virtually complete follow-up of the individuals. Participation date in HUNT2 was the baseline when individuals were considered at-risk, and were followed until their date of dementia diagnosis or dementia-related mortality until 15th February 2021 or 31st May 2020, respectively.

Statistical analysis

Descriptive data are presented as mean (standard deviation [SD]) for continuous variables and number (percentage) for categorical variables. To assess the association between change in PAI score and dementia, the following categories between HUNT1 and HUNT2 were used: 0 at both HUNT1 and HUNT2; 0 to ≤50, 0 to 51−99, and 0 to ≥100 from HUNT1 to HUNT2, respectively; ≤50 at both HUNT1 and HUNT2, ≤50 to 0, ≤50 to 51−99, and ≤50 to ≥100 from HUNT1 to HUNT2, respectively; 51−99 at both HUNT1 and HUNT2, 51−99 to 0, 51−99 to ≤50, and 51−99 to ≥100 from HUNT1 to HUNT2, respectively; ≥100 at both HUNT1 and HUNT2, ≥100 to 0, ≥100 to ≤50, and ≥100 to 51−99 from HUNT1 to HUNT2, respectively. Further, we categorized study individuals into PAI scores <100 and ≥100 groups and used the following
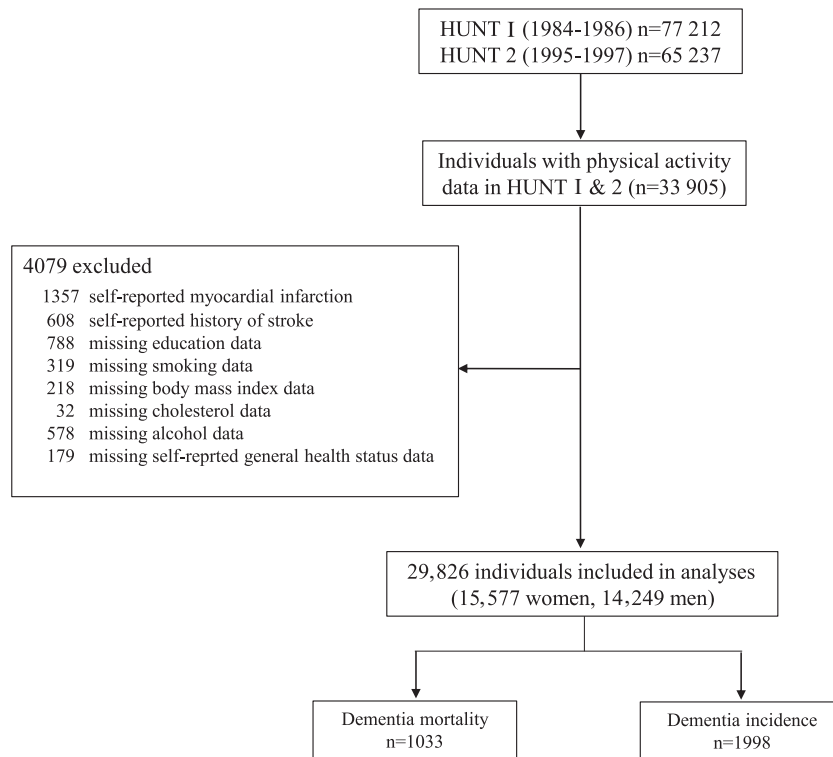
Figure 1. Study profile. We estimated PAI scores in individuals who took part in HUNT1 and HUNT2 and subsequently linked these data to dementia incidence from local dementia registries, and dementia-related mortality from the Norwegian Cause of Death Registry.

categories of change between HUNT1 and HUNT2: <100 at both HUNT1 and HUNT2, <100 at HUNT1 and ≥100 at HUNT2, ≥100 at HUNT1 and <100 at HUNT2, and ≥100 at both HUNT1 and HUNT2. Selection of these cut points was made 'a priori' based on previous studies.[18,23,24] We used Cox proportional hazard regression analyses to investigate the association between changes in PAI score and dementia incidence and dementia-related mortality. Results are reported as adjusted hazard ratios (aHR) with 95% confidence intervals (CI). Basic models were adjusted for sex and age (stratified by 5-year age-at-risk intervals which is a time-varying covariate determining the current risk rather than the age when the risk factor was assessed). Accordingly, with increasing age during the follow-up period, an individual (man or woman) may contribute to more than one 'at-risk' group, defined by age and sex. The final multivariable adjusted model further included body mass index (18.5−24.9, 25−29.9, or ≥30 kg/m²), smoking status (former, current, or never), hypertension (yes [systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or taking blood pressure medications], or no), diabetes status (yes [self-reported history of diabetes or non-fasting serum glucose >11.1 mmol/L], or no), elevated serum cholesterol (yes [age-based serum cholesterol levels: >6.1 mmol/L

for those <30 years, >6.9 mmol/L for those between the ages of 30 and 49, >7.8 mmol/L for those ≥50 years], or no), alcohol consumption (abstainer, 0 to ≤7 drinks, >7 to ≤14 drinks, or >14 drinks over a 2-week period), marital status (married, un-married, divorced/separated, or widow/widower), education attainment (<10, 10−12, or ≥13 years), general health status (bad, not so good, good, or very good), and family history of stroke (yes, no). The proportional hazard assumption was examined and satisfied with the use of Schoenfeld residuals, and the log-log plots both for dementia incidence and mortality. Results of time-to-event analyses were also reported with Kaplan-Meier survival plots.

We also estimated the change in PAI as a continuous variable, that is, the difference between HUNT2 and HUNT1 divided by the number of years between the 2 examinations. The squared value of PAI change was used to examine the nonlinear trend and to assess the association between annual change in PAI and dementia.

We also estimated the metabolic equivalent of task (MET)-hours per week based on the responses to PA questions at both HUNT1 and HUNT2 and divided individuals according to whether or not they performed ≥7.5 MET-hours per week (the lower limit of the current PA

recommendations, 150 min of moderate or 75 min of vigorous-intensity PA). Further, we assessed the combined effect of change in weekly PAI score and change in MET-hours per week on dementia incidence and mortality. Individuals with a weekly PAI score ≥100 and ≥7.5 MET-hours per week at both HUNT1 and HUNT2 served as the reference cohort. In a separate analysis, we used Laplace regression adjusted for age and sex to estimate the years of life gained as the difference in survival years associated with different PAI change groups.[25,26] We also performed sensitivity analyses to examine the robustness of our findings by excluding the events that occurred during the first 5 years of follow-up to minimize the likelihood of bias due to reverse causality. Analyses were also conducted in subgroups of individuals, i.e., current smokers, obese and hypertensive patients. All statistical tests were 2-sided, and $P<0.05$ was considered statistically significant. The statistical analyses were conducted using Stata statistical software, version 16 (StataCorp, Texas, USA).

Role of the funding source

The funder of the study had no role in study design, analysis or interpretation of data, or writing of the report. The corresponding author (UW), ART and JN had full access to all data in the study, and UW had the final responsibility for the decision to submit for publication.

Results

Characteristics of individuals according to PAI and temporal changes in PAI are presented in Table 1, and in supplementary Tables (sTables 1−3). The mean age of individuals at HUNT2 who had a PAI score <100 at both assessments was 55.1 years (SD 13.4), and 49.6 years (SD 11.0) for individuals with ≥100 at both HUNT1 and HUNT2. Individuals who had a PAI score <100 at both assessments demonstrated an unfavourable health profile as compared with those who maintained ≥100. For example, those with a PAI score <100 at both HUNT1 and HUNT2 had higher cholesterol levels, weighed more, were less educated, and had a high prevalence of current smoking, hypertension, and diabetes compared with those who achieved ≥100 at both assessments (Table 1). A detailed description of the individual's characteristics according to change in PAI and participation in the two HUNT waves is presented in sTable 3. Across all categories of PAI change, the prevalence of obesity and hypertension increased from HUNT1 to HUNT2. Furthermore, highly educated individuals were more likely to sustain a high PAI score at the two time points.

The baseline characteristics of individuals are also presented both for dementia incidence and mortality in sTable 4. Those who were diagnosed with dementia in later years were older and less educated, had higher cholesterol levels, and higher prevalence of hypertension and diabetes, and a high percentage of these individuals reported 'bad or not so good' on self-rated health status. We also compared the 4079 individuals who were excluded with those who were included in the study analyses. As expected, the excluded individuals were older, had higher prevalence of obesity, hypertension, diabetes, and were less educated compared to those who were included in the study (sTable 5).

Among 1998 incident cases of dementia, the median follow-up was 24.5 years (interquartile range: 24.1−25.0). Multivariable-adjusted analyses showed that individuals who maintained a PAI score ≥100 at both assessments, or those who increased their PAI score over time had reduced risk of incident dementia (Tables 2 & 3). Compared with inactive (0 PAI) at both HUNT1 and HUNT2, aHRs were 0.75 (95% CI: 0.58−0.97) for individuals with ≥100 PAI at both assessments, 0.66 (95% CI: 0.50−0.89) for those who increased their PAI score over time (0 at HUNT1 and ≥100 at HUNT2), 0.81 (95% CI: 0.66−1.00) for those who increased from 0 PAI at the first assessment to ≤50 at the second assessment, and 0.59 (95% CI: 0.43−0.80) among individuals who increased from 0 PAI at the first assessment to 51−99 PAI at the second assessment (Table 2).

We found an inverse association between change in PAI and incident dementia when using change in PAI between HUNT1 and HUNT2 as a continuous variable ($P=0.005$ for linear trend and $P=0.63$ for quadratic trend). The aHR associated with an annual increase of 10 PAI was 0.89 (95% CI: 0.84−0.95) for incident dementia (sFigure 1). For dementia-related mortality, we observed a similar, although, weaker relation (aHR: 0.94, 95% CI: 0.87−1.03).

Using a PAI score <100 at both assessments as the reference cohort, aHRs for incident dementia were 0.82 (95% CI: 0.69−0.99) for those with ≥100 at both HUNT1 and HUNT2, and 0.83, 95% CI: 0.72−0.96) for individuals who increased from <100 at HUNT1 to ≥100 at HUNT2 (Table 3, Figure 2).

Compared with individuals with a PAI score <100 at both assessments, those who increased their PAI scores over time (<100 at HUNT1 and ≥100 at HUNT2) gained 2.8 (95% CI: 1.3−4.2, $P<0.001$) dementia-free years. The corresponding dementia-free years for individuals with a PAI score ≥100 at both assessments were 3.0 (95% CI: 1.3−4.8, $P=0.001$) (Table 3).

During the median follow-up of 23.6 years (interquartile range: 20.8−24.2), there were 1033 dementia-related deaths. An increase in PAI and a sustained high PAI score over time were associated with a reduced risk of dementia-related mortality (Tables 2 & 3). Compared with inactive (0 PAI) at both HUNT1 and HUNT2, aHRs were 0.62 (95% CI: 0.43−0.91) for individuals who sustained a high PAI score (≥100) at both time

HUNT 1 PAI	<100		≥100		P-value[†]
HUNT 2 PAI	**<100**	**≥100**	**<100**	**≥100**	
No. of individuals	19,366	4207	3312	2941	
Female sex, No. (%)	11,310 (58.4)	1906 (45.3)	1494 (45.1)	867 (29.5)	
Age, mean (SD), years	55.1 (13.4)	49.6 (11.5)	52.0 (12.8)	49.6 (11.0)	<0.0001
Body mass index[††], mean (SD), kg/m²	26.8 (4.1)	26.2 (3.6)	26.6 (3.8)	25.7 (3.1)	<0.0001
Body mass index, No. (%)					
<18.5	102 (0.5)	15 (0.4)	9 (0.3)	6 (0.2)	
18.5−24.9	6722 (34.7)	1672 (39.7)	1182 (35.7)	1279 (43.5)	
25.9−29.9	8855 (45.7)	1950 (46.4)	1569 (47.4)	1382 (47.0)	
≥30	3587 (19.1)	570 (13.5)	552 (16.6)	274 (9.3)	<0.0001
Total cholesterol, mean (SD), mmol/L	6.2 (1.2)	5.9 (1.1)	6.0 (1.2)	5.8 (1.1)	<0.0001
High cholesterol[‡], No. (%)					
Yes	2320 (12.0)	396 (9.6)	355 (10.7)	234 (8.0)	
No	17,046 (88.0)	3811 (90.6)	2957 (89.3)	2707 (92.0)	<0.0001
Systolic BP, mean (SD), mmHg	140.4 (22.2)	135.7 (19.5)	138.0 (20.4)	135.6 (18.4)	<0.0001
Diastolic BP, mean (SD), mmHg	82.3 (11.9)	80.5 (11.6)	82.1 (11.6)	80.8 (11.1)	<0.0001
Hypertension status[‡‡], No. (%)					
Yes	9850 (50.9)	1714 (40.7)	1550 (46.8)	1161 (39.5)	
No	9516 (49.1)	2493 (59.3)	1762 (53.2)	1780 (60.5)	<0.0001
Serum glucose, mean (SD), mmol/L	5.5 (1.5)	5.4 (1.2)	5.5 (1.4)	5.3 (1.2)	<0.0001
Diabetes status[¶], No. (%)					
Yes	656 (3.4)	97 (2.3)	76 (2.3)	45 (1.5)	
No	18,710 (96.6)	4110 (97.7)	3236 (97.7)	2896 (98.5)	<0.0001
Smoking status, No. (%)					
Never	7630 (39.4)	1575 (37.4)	1478 (44.6)	1565 (53.2)	
Current	5894 (30.4)	1186 (28.2)	812 (24.5)	464 (15.8)	
Former	5842 (30.2)	1446 (34.4)	1022 (30.9)	912 (31.0)	<0.0001
Education, No. (%)					
<10 y	9119 (47.1)	1272 (30.3)	1127 (34.0)	659 (22.4)	
10-12 y	6642 (34.3)	1679 (39.9)	1194 (36.1)	1088 (37.0)	
>12 y	3605 (18.6)	1254 (29.8)	991 (29.9)	1194 (40.6)	<0.0001
Alcohol consumption[‖], No. (%)					
0	2707 (14.0)	327 (7.8)	246 (7.4)	185 (6.3)	
0 to ≤7	14 779 (76.3)	3255 (77.4)	2597 (78.4)	2217 (75.4)	
>7 to ≤14	1519 (7.8)	495 (11.8)	395 (11.9)	416 (14.1)	
>14	361 (1.9)	130 (3.0)	74 (2.2)	123 (4.2)	<0.0001
Self-rated health status, No. (%)					
Bad/not so good	6124 (31.6)	745 (17.7)	788 (23.8)	381 (12.9)	
Good/very good	13,242 (68.4)	3462 (82.3)	2524 (76.2)	2560 (87.1)	<0.0001
Family history stroke, No. (%)					
Yes	4646 (23.8)	879 (20.9)	755 (22.8)	610 (20.7)	
No	14,750 (76.2)	3328 (79.1)	2557 (77.2)	2331 (79.3)	<0.0001

***Table 1*: Characteristics of Individuals according to temporal changes in Personal Activity Intelligence.**

PAI, Personal Activity Intelligence; HUNT, The Trøndelag Health Study.

[†] For linear trend, regression analyses were used for continuous variables; χ^2 tests were used for proportions of categorical variables.

[††] Calculated as weight in kilograms divided by height in meters squared.

[‡] Age specific high cholesterol levels: >6.9 mmol/L for individuals under 50 years, and >7.8 mmol/L for individuals ≥50 years.

[‡‡] Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or taking blood pressure medications.

[¶] Diabetes was defined as non-fasting serum glucose levels >11.1 mmol/L and/or reported history of diabetes.

[‖] Based on consumption over a 2-week period.

points, 0.71 (95% CI: 0.53−0.96) for those who increased from 0 at first assessment to a PAI score ≤50 at the second assessment, and 0.50 (95% CI: 0.32 −0.80) for those who increased from 0 at first assessment to a PAI score ≥100 at the second assessment (Table 2).

Compared with the individuals who had a PAI score <100 at both HUNT1 and HUNT2, aHRs for dementia-

	Dementia incidence				Dementia-related mortality			
	HUNT2				HUNT2			
	0 PAI	≤50 PAI	51−99 PAI	≥100 PAI	0 PAI	≤50 PAI	51−99 PAI	≥100 PAI
HUNT1								
0 PAI								
Events	111	453	63	79	57	214	34	27
aHR (95% CI)[a]	1.00	0.76	0.52	0.58	1.00	0.69	0.67	0.46
	(Reference)	(0.62−0.94)	(0.38−0.71)	(0.44−0.78)	(Reference)	(0.52−0.93)	(0.44−1.03)	(0.29−0.73)
aHR (95% CI)[b]	1.00	0.81	0.59	0.66	1.00	0.71	0.72	0.50
	(Reference)	(0.66−1.00)	(0.43−0.80)	(0.50−0.89)	(Reference)	(0.53−0.96)	(0.47−1.10)	(0.32−0.80)
≤50 PAI								
Events	54	512	72	82	40	323	40	42
aHR (95% CI)[a]	1.57	1.10	0.5	0.74	1.61	1.01	0.71	0.68
	(1.13−2.17)	(0.90−1.36)	(0.49−0.88)	(0.56−0.98)	(1.07−2.42)	(0.76−1.35)	(0.47−1.06)	(0.46−1.02)
aHR (95% CI)[b]	1.43	1.16	0.77	0.87	1.56	1.03	0.77	0.75
	(1.03−1.99)	(0.94−1.43)	(0.57−1.04)	(0.65−1.16)	(1.04−2.34)	(0.78−1.38)	(0.51−1.16)	(0.50−1.12)
51−99 PAI								
Events	10	117	30	47	7	58	12	19
aHR (95% CI)[a]	1.17	0.90	0.63	0.67	1.90	0.78	0.56	0.60
	(0.61−2.23)	(0.69−1.16)	(0.42−0.94)	(0.47−0.94)	(0.87−4.16)	(0.54−1.13)	(0.30−1.04)	(0.36−1.01)
aHR (95% CI)[b]	1.21	1.05	0.78	0.81	1.66	0.84	0.66	0.68
	(0.63−2.31)	(0.81−1.37)	(0.52−1.16)	(0.57−1.16)	(0.75−3.65)	(0.58−1.21)	(0.35−1.24)	(0.40−1.15)
≥100 PAI								
Events	15	168	48	137	8	76	15	61
aHR (95% CI)[a]	1.12	0.94	0.63	0.59	1.33	0.78	0.41	0.54
	(0.65−1.91)	(0.74−1.19)	(0.45−0.88)	(0.46−0.76)	(0.63−2.78)	(0.55−1.10)	(0.23−0.73)	(0.38−0.78)
aHR (95% CI)[b]	1.07	1.08	0.82	0.75	1.26	0.86	0.47	0.62
	(0.63−1.84)	(0.85−1.38)	(0.58−1.16)	(0.58−0.97)	(0.60−2.65)	(0.61−1.22)	(0.26−0.83)	(0.43−0.91)

***Table 2**: Hazard ratio of dementia incidence and mortality by changes in Personal Activity Intelligence.*
PAI, Personal Activity Intelligence; HUNT, The Trøndelag Health Study; aHR, adjusted hazard ratio; CI, confidence interval.
 [a] Adjusted for age and sex.
 [b] Adjusted for age, sex, body mass index, smoking status, hypertension, diabetes, serum cholesterol, alcohol consumption, marital status, education attainment, general health status, and family history of stroke.

related mortality were 0.73 (95% CI: 0.56−0.96) for those with ≥100 at both assessments, and 0.74 (95% CI: 0.59−0.92) for individuals who increased from <100 at HUNT1 to a PAI score ≥100 at HUNT2 (Table 3, Figure 3). When adjusted for age and sex, individuals with high PAI scores (≥100) at both HUNT1 and HUNT2 gained 2.6 (95% CI: 0.9−4.3, P=0.003) years of life, compared to individuals with <100 at both assessments (Table 3). For those who increased their PAI score over time (<100 at HUNT1 and ≥100 at HUNT2), the corresponding years gained were 2.4 (95% CI: 1.0−3.8, P=0.001).

After excluding the first 5 years of follow-up, there were 1799 incident dementia cases and 992 events of dementia-related mortality. The results of these analyses did not materially differ from our primary analyses. In subgroups of individuals, change in PAI score over the years was predictive of dementia incidence and dementia-related mortality. For example, compared with hypertensive individuals with a PAI score <100 at both HUNT1 and HUNT2, the aHRs for hypertensive

individuals with PAI ≥100 at both assessments was 0.74 (95% CI: 0.58−0.94) for incident dementia, and 0.68 (95% CI: 0.48−0.96) for dementia-related mortality. There were fewer events for incident dementia and dementia-related mortality in the corresponding PAI change categories among smokers and obese individuals. The aHRs associated with PAI ≥100 at both assessments for dementia-related mortality were 0.88 (95% CI: 0.42−1.83) in smokers, and 0.80 (95% CI: 0.36−1.74) in obese individuals, compared with those with a PAI score of <100 at both HUNT1 and HUNT2 (sTable 6). Of interest, compared with individuals with a PAI score ≥100 and meeting the PA recommendations (defined as ≥7.5 MET-hours per week) at both time points, those with a PAI score <100 but ≥7.5 MET-hours at both time points demonstrated an increased risk of incident dementia (aHR 2.38, 95% CI 1.71−3.33; sTable 7) and dementia-related mortality (aHR 2.42, 95% CI 1.56−3.75; sTable 8). Furthermore, individuals who increased their weekly MET-hours from <7.5 in HUNT1 to ≥7.5 in HUNT2 but had a weekly PAI score

|	Dementia incidence		Dementia-related mortality	
	HUNT2		HUNT2	
	<100 PAI	≥100 PAI	<100 PAI	≥100 PAI
HUNT1				
<100 PAI				
Events	1422	208	785	88
aHR (95% CI)[a]	1.00	0.76	1.00	0.69 (0.55-0.86)
	(Reference)	(0.66−0.88)	(Reference)	
aHR (95% CI)[b]	1.00	0.83	1.00	0.74
	(Reference)	(0.72−0.96)	(Reference)	(0.59−0.92)
Years delayed/gained[c]	Reference	2.8 (1.3−4.2)	Reference	2.4 (1.0−3.8)
≥100 PAI				
Events	231	137	99	61
aHR (95% CI)[a]	0.99	0.69	0.83	0.65 (0.50-0.85)
	(0.86−1.14)	(0.58−0.82)	(0.68−1.03)	
aHR (95% CI)[b]	1.09	0.82	0.90	0.73
	(0.95−1.26)	(0.69−0.99)	(0.73−1.11)	(0.56−0.96)
Years delayed/gained[c]	−0.4 (−1.7 to 1.0)	3.0 (1.3−4.8)	0.9 (−0.4 to 2.2)	2.6 (0.9−4.3)

***Table 3*: Dementia incidence and mortality by changes in Personal Activity Intelligence.**
PAI, Personal Activity Intelligence; HUNT, The Trøndelag Health Study; aHR, adjusted hazard ratio; CI, confidence interval.
  [a] Adjusted for age and sex.
  [b] Adjusted for age, sex, body mass index, smoking status, hypertension, diabetes, serum cholesterol, alcohol consumption, marital status, education attainment, general health status, and family history of stroke.
  [c] Estimates are for number of dementia-free years, and years gained for dementia mortality, adjusted for age and sex.
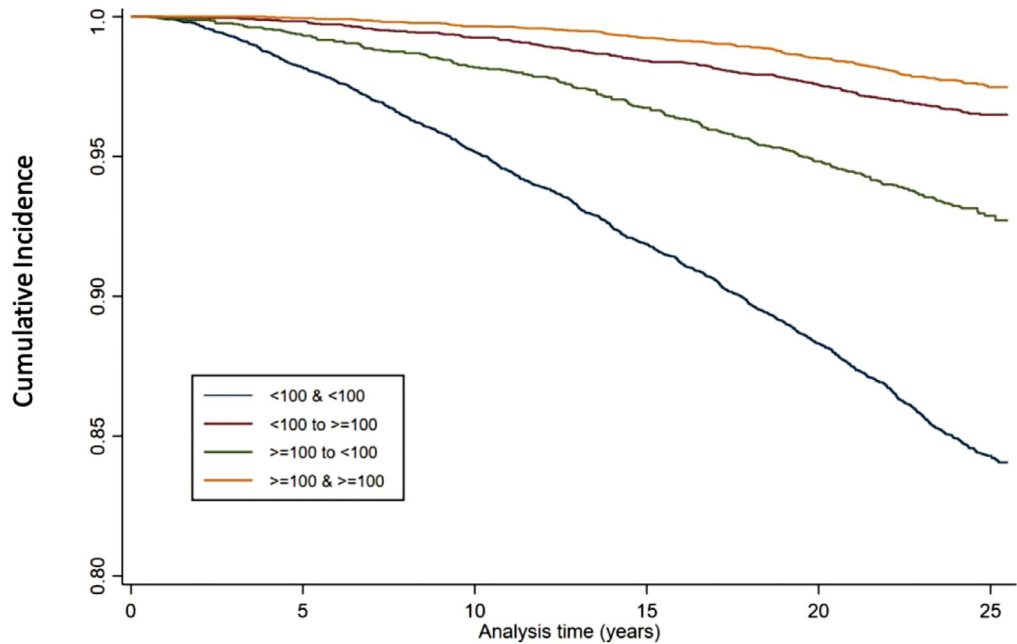
Figure 2. Dementia Incidence by change in Personal Activity Intelligence. PAI=Personal Activity Intelligence.

<100 on both time points had increased risk of incident dementia (aHR 1·40, 95% CI 1·14−1·73; sTable 7) and mortality (aHR 1·48, 95% CI 1·08−2·03; sTable 8) when compared to those with a PAI score ≥100 who met the PA recommendations at both time points.

Discussion

In this large prospective study of healthy men and women at baseline, we found that maintaining high weekly PAI scores and an increase in PAI scores over time were associated with a reduced risk of incident dementia, dementia-related mortality, and delayed onset of dementia outcomes when compared with habitually inactive individuals or those with low weekly PAI scores.

Our findings are compatible with previous studies investigating the role of leisure-time PA on the incidence of dementia or Alzheimer's disease.[3-5] In a sub-cohort of 4633 individuals (mean age 60 years), persistent high levels of leisure-time PA assessed over 6 years were associated with a lower rates of dementia incidence (aHR, 0·71; 95% CI, 0·54−0·92).[3] Similarly, compared with those who reported habitually low levels of PA, increased (aHR, 0·60: 95% CI, 0·36−0·99) and sustained high (aHR, 0·28; 95% CI, 0·08−0·94) levels of leisure-time PA throughout life among older adults (mean age 75 years) were associated with reduced risk of incident Alzheimer's disease.[4]

The WHO guidelines[13] for risk reduction of cognitive decline and dementia recommend PA engagement to reduce cognitive decline, and suggest that the beneficial effects of PA are largely due to aerobic exercise. This may be due to the beneficial effects of aerobic exercise on CRF, which is potentially a key target for improved brain health.[27] Considering the metabolic metric PAI (which is largely based on daily variations in heart rate) is strongly correlated with objectively measured CRF,[14] weekly PAI scores may complement, and improve, the WHO's recommendations for dementia prevention. The observation that a modest annual increase of just 10 PAI units is associated with a reduced risk of dementia (aHR, 0·89: 95% CI, 0·84−0·95) is consistent with previously obtained longitudinal data showing that a 1 MET increase in CRF over time reduces risk of incident dementia (aHR, 0·84; 95% CI, 0·75−0·93).[9]

Our findings show that obtaining a weekly PAI score of 100 was associated with similar risk reductions regardless of meeting the lower limits of PA recommendations or not. These results are not surprising because at similar intensities, a higher volume of PA is needed to achieve 100 weekly PAI than 7.5 MET-hours. Previously, we have shown that the 100 weekly PAI goal may fit well with the upper limit of current PA recommendations.[18] Importantly, we also observed that an increase in weekly PAI score from 0 to ≤50 and from 0 to 51−99 comparing baseline values versus the second assessment, was associated with risk reduction of dementia

incidence and dementia-related mortality. These results suggest that small increases in active time above the relative heart rate threshold where one starts to earn PAI[15] may be adequate to substantially reduce dementia risk. This is potentially a very impactful public health message and may be particularly useful in transitioning those who are habitually sedentary to some level of PA to confer significant health benefits. In practical terms, performing 150 weekly minutes of moderate-intensity exercise corresponds to 50-<100 PAI points, depending upon age and fitness level of the individual. For instance, in an unfit individual, 8−10 daily minutes of moderate-intensity exercise may be enough to obtain a weekly PAI score of 50. This PA volume should be attainable for most inactive individuals, and may encourage them to take up exercise and maintain an active routine with the aim of obtaining high weekly PAI scores. The recommended PAI score of ≥100 can be achieved by a combination of exercises at varying intensities according to personal preference, with higher intensities requiring less exercise time.

Our findings of delay in dementia onset and years of life gained associated with increase in PAI or sustained high PAI scores are of particular interest, considering that therapeutic interventions that can delay the onset and progression of Alzheimer's disease by one year could lower the prevalence of the disease by more than 9 million cases in 2050.[28] Although, ours is not a cause-and-effect study, these results are in keeping with numerous other studies, and further strengthen the contention that PA interventions protect against dementia and should be prescribed universally.

PAI can provide readily available and quantifiable feedback on an individual's PA level which in turn could serve as an important tool in health management among clinicians and the patients they serve. Keeping with that, in an exploratory study conducted in conjunction with cardiac rehabilitation in Australia, the use of PAI, incorporated in an App and a wearable heart rate monitor, served as a motivator for PA.[29] Cardiac patients who used PAI during the last 3 weeks of a 6-week intervention were found to be more physically active than those not using PAI.[29] Others demonstrated that individuals with type 2 diabetes using PAI (PAI-App and wearable heart rate monitor) over 12 weeks significantly increased their exercise capacity and sleep time, and decreased body fat percentage and sex-specific adiposity when compared with their peers following contemporary PA recommendations.[16] The introduction of PAI in everyday life has the potential to turn a theoretical association of PA into a daily encouraging process through monitoring and challenging the device-wearer to achieve a practical goal every day. Sharing this metric with physicians may motivate and encourage patients to augment their PA to increase weekly PAI scores. Such tactics may potentially enhance public health and reduce the risk of dementia. Further studies are needed to test this potential in diverse large populations.

The main strengths of the current study include a large sample size with a longitudinal study design, assessment of PAI at 2 time points 10 years apart, a comprehensive source of information on possible confounders, and meticulously documented dementia outcomes.

Our study has some limitations that we should acknowledge. First, we were not able to stratify dementia cases by specific subtypes; therefore, the associations between PAI and dementia incidence and mortality may not apply to all types of dementia. Second, our findings are not causal because of the observational nature of the study. Third, self-reported data were used to estimate PAI which may be prone to information bias. However, the validity and reliability of the PA questionnaires has been tested and found to be reproducible in numerous other studies.[30,31] Further, measurement errors and the nature of misclassification in a prospective study design such as ours are likely to be non-differential in relation to future disease and may underestimate the effects. Fourth, although the results have been adjusted for possible confounders and individuals with comorbid conditions were excluded at baseline, residual unmeasured or unknown variables such as prescribed medications, dietary practices and supplements, as well as biological and social factors may have influenced our estimates. Although, national statistics and epidemiologic data suggest that total energy intake in Norway during the past decades is relatively stable, however, a considerable proportion of individuals do not meet the nutritional recommendations of intakes of saturated fats, fibre and vitamin D.[32,33] Nevertheless, dietary data are difficult to analyse and interpret in epidemiological studies and, therefore, should be interpreted with caution. Fifth, despite a large study population, the precision of some effect estimates may be affected due to fewer events in certain sub-groups with restricted statistical power. Sixth, commonly, there is uncertainty associated with the cause of death stated by the doctor, and the precision is most probably particularly low when it comes to dementia for several reasons. While Alzheimer's disease accounts for 60−70% of dementia cases, this condition is only specified in 28% of death reports. Many patients with dementia are old and frail nursing home residents, and often have other illnesses that may have contributed to the death, which may be difficult to diagnose due to the patient's condition. The possibility of getting a thorough understanding of what lies behind the death may thus be limited, and dementia deaths may be under-reported. Seventh, observational studies may be subject to reverse causation bias especially with changes in PA in the preclinical phase of dementia. However, we observed no meaningful changes in the estimates after excluding events that occurred during the first 5 years of follow-

up. Finally, we studied a relatively homogenous and predominantly Caucasian population which limits the generalizability of our findings to other cohorts. Of note, a recent study among healthy Chinese adults[34] and an American cohort[19] reported an inverse association between PAI (with the same cut-off values for PAI as used in this study) and all-cause mortality and CVD outcomes, suggesting that PAI has prognostic significance in diverse settings. Nonetheless, additional studies of the PAI metric, including validation of its cut-off values, in different races and ethnicities with varying degrees of underlying risk are warranted before generalizability of these results can be assumed.

Conclusion
In this large, prospective study of relatively healthy individuals, maintaining high weekly PAI scores and an increase in PAI scores over time were associated with a reduced risk of incident dementia and dementia-related mortality, along with delay in dementia onset and years of life gained. These findings add support and extend the scientific evidence related to the importance of PA as a key modifiable risk factor for the prevention of dementia.

Contributors
ART, JN, and UW verified the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. ART, JN, and UW designed the study. ART and JN analysed and interpreted the data. IB and ES oversee the local registries providing incidence-data. ART, JN and UW drafted the manuscript. ART, JN, UW, GS, SB, HS, RES, BAF, MZ, SL, AKF and AMH critically revised the manuscript. UW and JN supervised the study. ART and UW obtained funding. All authors were responsible for the decision to submit the manuscript.

Data sharing statement
The Trøndelag Health Study (HUNT) has invited individuals residing in the Trøndelag county in the central Norway to participate in four surveys between 1984 and 2019. Comprehensive data from more than 140,000 individuals having participated at least once and biological material from 78,000 individuals are collected. The data are stored in HUNT databank and biological material in HUNT biobank. HUNT Research Centre has permission from the Norwegian Data Inspectorate to store and handle these data. The key identification in the data base is the personal identification number given to all Norwegians at birth or immigration, whilst de-identified data are sent to researchers upon approval of a research protocol by the Regional Ethical Committee and HUNT Research Centre. To protect participants' privacy, HUNT Research Centre aims to limit storage of data outside HUNT databank and cannot deposit data in open repositories. HUNT databank has precise

information on all data exported to different projects and are able to reproduce these on request. There are no restrictions regarding data export given approval of applications to HUNT Research Centre. For more information see: http://www.ntnu.edu/hunt/dat.

Declaration of interests
Professor Wisløff is the inventor of PAI, and scientific advisor of a company (PAI Health inc) that holds the IP rights for PAI that develops applications that utilize data from diverse heart rate monitors to display PAI for users. Due to the potential conflict of interest, Wisløff did not take part in any of the statistical analysis in the current study. All other authors declare no competing interests.

Acknowledgments

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101607.

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