Temporal changes in cardiorespiratory fitness and risk of dementia incidence and mortality: a population-based prospective cohort study

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Summary

Background Cardiorespiratory fitness is associated with risk of dementia, but whether temporal changes in cardiorespiratory fitness influence the risk of dementia incidence and mortality is still unknown. We aimed to study whether change in estimated cardiorespiratory fitness over time is associated with change in risk of incident dementia, dementia-related mortality, time of onset dementia, and longevity after diagnosis in healthy men and women at baseline.

Methods We linked data from the prospective Nord-Trøndelag Health Study (HUNT) done in Nord-Trøndelag, Norway with dementia data from the Health and Memory Study and cause of death registries (n=30 375). Included participants were apparently healthy individuals for whom data were available on estimated cardiorespiratory fitness and important confounding factors. Datasets were matched to each participant through their 11-digit personal identification number. Cardiorespiratory fitness was estimated on two occasions 10 years apart, during HUNT1 (1984–86) and HUNT2 (1995–97). HUNT2 was used as the baseline for follow-up. Participants were classified into two sex-specific estimated cardiorespiratory fitness groups according to their age (10-year categories): unfit (least fit 20% of participants) and fit (most fit 80% of participants). To assess the association between change in estimated cardiorespiratory fitness and dementia, we used four categories of change: unfit at both HUNT1 and HUNT2, unfit at HUNT1 and fit at HUNT2, fit at HUNT1 and unfit at HUNT2, fit at both HUNT1 and HUNT2. Using Cox proportional hazard analyses, we estimated adjusted hazard ratios (AHR) for dementia incidence and mortality related to temporal changes in estimated cardiorespiratory fitness.

Findings During a median follow-up of 19·6 years for mortality, and 7·6 years for incidence, there were 814 dementia-related deaths, and 320 incident dementia cases. Compared with participants who were unfit at both assessments, participants who sustained high estimated cardiorespiratory fitness had a reduced risk of incident dementia (AHR 0·60, 95% CI 0·36–0·99) and a reduced risk of dementia mortality (0·56, 0·43–0·75). Participants who had an increased estimated cardiorespiratory fitness over time had a reduced risk of incident dementia (AHR 0·52, 95% CI 0·30–0·90) and dementia mortality (0·72, 0·52–0·99) when compared with those who remained unfit at both assessments. Each metabolic equivalent of task increase in estimated cardiorespiratory fitness was associated with a risk reduction of incident dementia (adjusted HR 0·84, 95% CI 0·75–0·93) and dementia mortality (0·90, 0·84–0·97). Participants who increased their estimated cardiorespiratory fitness over time gained 2·2 (95% CI 1·0–3·5) dementia-free years, and 2·7 (0·4–5·8) years of life when compared with those who remained unfit at both assessments.

Interpretation Change in estimated cardiorespiratory fitness is an independent risk factor for incidence dementia and dementia mortality. Maintaining or improving cardiorespiratory fitness over time may be a target to reduce risk of dementia incidence and mortality, delay onset, and increase longevity after diagnosis. Our data highlight the importance of assessing cardiorespiratory fitness in health risk assessment for people at risk of dementia.

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See **Comment** page e541

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Introduction

Dementia is a clinical syndrome that includes a broad category of complex brain diseases characterised by a progressive decline in cognitive functions that is severe enough to interfere with the ability to function independently.[1] As of 2017, there are 50 million people worldwide with dementia, which is estimated to increase to more than 150 million by 2050.[2] There is no available cure, and dementia is ultimately fatal. Median survival time after diagnosis is about 5 years for men and 7 years for women, varying with dementia type and age of onset.[3] Despite major efforts worldwide, the failure rate in dementia drug trials is 99·6%, which is higher than in any other disease area.[4] In recognition that the emphasis on a single hypothesis has not yielded positive outcomes, the field has gradually shifted the focus of research towards modifiable risk factors.[5,6] The rapidly growing literature suggests that regular physical

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Research in context

Evidence before this study

We searched PubMed for clinical and observational trials, meta-analyses, and review articles published between Oct 14, 2018, and April 15, 2019, using the following search terms: "cardiorespiratory fitness", "change in cardiorespiratory fitness", "dementia", "dementia incidence", "dementia mortality", "fitness and dementia risk". Our search yielded no previous studies on the association between temporal changes in cardiorespiratory fitness and dementia risk. However, a growing body of literature suggests that individuals with high age-relative cardiorespiratory fitness have substantial reduced risk of dementia when compared with unfit counterparts.

Added value of this study

To our knowledge, our study is the first to use longitudinal estimated cardiorespiratory fitness data in a large number of men and women that were healthy at baseline, together with detailed information on several potentially confounding factors collected up to three decades before dementia diagnosis, to assess the association between temporal changes in estimated cardiorespiratory fitness and the risk of dementia incidence, dementia mortality, number of disease-free years, and number of years of life gained. Previous studies mainly include data on only men or only women, and rely on a single assessment of cardiorespiratory fitness, making it difficult to account for confounding factors during follow-up. The availability of temporal changes in estimated cardiorespiratory fitness and data on both sexes make our data particularly strong.

Implications of all the available evidence

Our results highlight the modifiability of dementia risk, indicating that individuals might be able to decrease risk by attaining or sustaining a high age-relative estimated cardiorespiratory fitness, even after midlife. Furthermore, our data show the importance of cardiorespiratory fitness in health risk assessments, which should contribute to a step forward in new guidelines and recommendations for people at risk of dementia.

activity or high cardiorespiratory fitness, or both, attenuate cognitive impairment and reduce risk of dementia.[7–9]

Meta-analyses have shown that regular physical activity was associated with a risk reduction of about 30–40% in developing Alzheimer's disease, when compared with inactive counterparts.[10] Conversely, a systematic review[11] has suggested that the evidence of slowing cognitive decline and delaying onset of cognitive impairment and dementia relating to physical activity interventions is largely insufficient. Notably, evolving evidence suggests that cardiorespiratory fitness might be a more sensitive metric to predict health risk compared with self-reported physical activity.[12–14] In support of cardiorespiratory fitness as a so-called health predictor, several studies[12,15–18] show 36–88% reduction in risk of developing dementia among those with a high age-relative cardiorespiratory fitness compared with unfit counterparts. However, most of these studies rely on a single baseline assessment of cardiorespiratory fitness, making it difficult to account for potential confounding factors during follow-up. The seminal study by Blair and colleagues[19] showed that risk of all-cause mortality decreased by improving estimated cardiorespiratory fitness over time, but evidence is scarce on whether modifying estimated cardiorespiratory fitness affects dementia-related mortality, time for onset of disease, or longevity in apparently healthy individuals that eventually develop dementia. Here, we tested the hypothesis that change in estimated cardiorespiratory fitness over time is associated with change in risk of incident dementia, dementia-related mortality, time of onset of dementia, and longevity after diagnosis in healthy men and women at baseline.

Methods

Study design and participants

The HUNT study constitutes large total population-based cohorts from four health surveys—HUNT1 (1984–86), HUNT2 (1995–97), HUNT3 (2006–08), and HUNT4 (2017–19)—done in Nord-Trøndelag, Norway, in which participants are followed up longitudinally, and through several comprehensive national health registries. All citizens older than 20 years were invited to participate in all surveys, which involved clinical examinations and questionnaires pertaining to health status and lifestyle. To date, it is one of the most comprehensive databases for medical research, and detailed accounts for the HUNT surveys have been previously described in detail.[20]

In this study, we estimated cardiorespiratory fitness in participants who took part in both HUNT1 (recruitment: Jan 5, 1984, to Feb 15, 1986) and HUNT2 (recruitment: Aug 15, 1995, to June 18, 1997), and thereafter linked to incidence dementia data from the Health and Memory Study (HMS; recruitment: March 9, 1995, to July 14, 2010), and to dementia-related mortality from the Norwegian Cause of Death Registry that collects death certificates for all deaths in the country. These datasets can be matched to each participant through their 11-digit personal identification number. During 1995 to 2011, the HMS[21] was done in patients residing in nursing homes and in patients referred to memory clinics in Nord-Trøndelag, the same county where the HUNT surveys were done. About 90% of the participants in the HMS, who were later diagnosed with dementia (after HUNT2 participation, which was used as baseline for follow-up), also participated in the HUNT surveys. The HMS is one of a few studies on risk factors of dementia that provide predictive data collected three decades ago, allowing researchers to study temporal changes and link to disease outcomes.

This study was approved by the Data Inspectorate and the Regional Committee on Medical and Health Research Ethics of Norway (2015/2015/REK midt). All participants have provided written informed consent.

Dementia incidence

Detailed information of the HMS cohort is described elsewhere.[21] The 2017 Norwegian national guidelines on dementia state that uncomplicated dementia in those aged 65 years should be diagnosed in primary health care.[22] However, these guidelines had not been introduced when the participants with dementia in this study were assessed and diagnosed. Nord-Trøndelag county was among the first counties to establish memory clinics in the hospitals and people with dementia in Nord-Trøndelag were referred to the memory clinics for assessment. The assessment of all these patients was done according to a comprehensive, common protocol applied in memory clinics across Norway.[23] The distribution of aetiological diagnoses, as outlined by Bergh and colleagues,[21] shows that participation in HMS is not restricted to people with early onset dementia.

Dementia-related mortality

Of the 33 471 individuals who participated in both HUNT1 and HUNT2 and had cardiorespiratory fitness data available, we excluded 3096 participants from mortality follow-up owing to missing data and self-reported history of myocardial infarction or stroke. 30 375 participants (15 925 women and 14 450 men) were included in our analyses of dementia-related mortality (figure 1).

We compared participants who were included in our study analyses with those who were excluded (appendix p 2).

Endpoints and follow-up

The HUNT data were linked to the hospital HMS data collected between 1995 and 2010. Data on the cause and date of death were obtained from the Norwegian Cause of Death Registry, and matched to each participant through their 11-digit personal identification number. Dementia-related mortality was identified when it was either the underlying, immediate, or accompanying cause of death (as defined in the International Classification of Diseases, 9th revision: 290·0–290·9, 294·2, 331, or 10th revision: F00-F03 and G30·0–G30·9). Our study had a virtually complete follow-up of participants, because registration in the population registers is mandatory in Norway. Only participants who emigrated from the country are missing in the analyses (<1%). Baseline was defined as the date of participation in HUNT2 and participants were followed up until their date of death or the end of follow-up on May 31, 2016.

Cardiorespiratory fitness

A non-exercise prediction model was used for estimated cardiorespiratory fitness.[24] The sex-specific models consisted of age, adiposity measures, physical activity, and resting heart rate, and provided estimated cardiorespiratory fitness values in ml/kg/min. A detailed account of the derivation and validation of these prediction models is described elsewhere.[25,26] Participants were further classified into two sex-specific estimated cardiorespiratory fitness groups according to their age (10-year categories): unfit (least fit 20% of participants) and fit (most fit 80% of participants).[14]

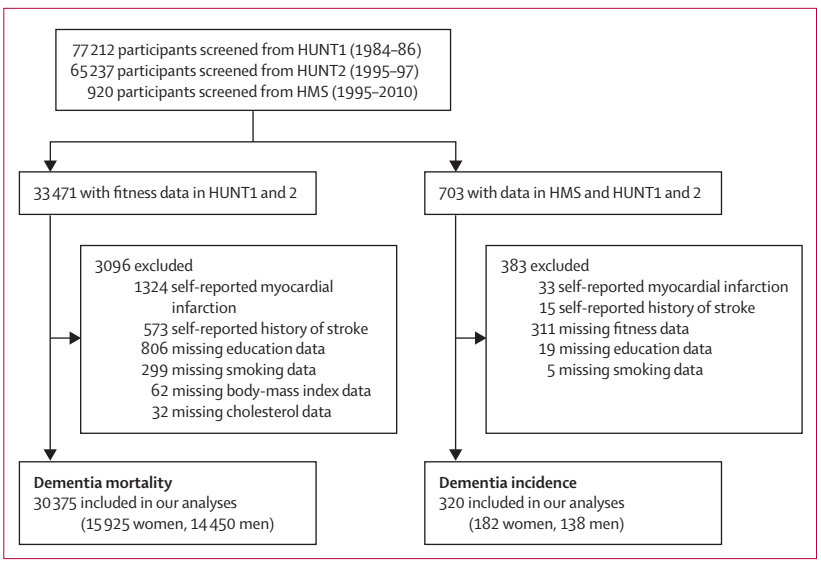

Figure 1: **Study profile**
We estimated cardiorespiratory fitness in participants who took part in both HUNT1 and HUNT2 and subsequently linked these data to dementia incidence data from the HMS and to dementia-related mortality from the Norwegian Cause of Death Registry. HMS= Health and Memory Study.

See **Online** for appendix

Statistical analysis

Descriptive data are shown as mean (SD) for continuous variables and number (%) for categorical variables. We compared baseline characteristics using χ^2 test for categorical variables and using Student's *t* test and linear regression analysis for continuous variables. To assess the association between change in estimated cardiorespiratory fitness and dementia, we used four categories of change: unfit at both HUNT1 and HUNT2, unfit at HUNT1 and fit at HUNT2, fit at HUNT1 and unfit at HUNT2, fit at both HUNT1 and HUNT2. We used Cox proportional hazard regression analyses to assess the association between estimated cardiorespiratory fitness change and dementia incidence and dementia-related mortality. Three timepoints were available to use in the Cox regression analysis for incident dementia: first contact with doctor, first contact at hospital, and date of valid diagnosis at hospital. In the Cox regression analysis, whichever timepoint came first for the participants was used. The proportional hazard assumption was satisfied with the use of Schoenfeld residuals. The basic models were adjusted for age and sex, and results are reported as hazard ratios (HRs) with 95% CIs after further multivariable adjustment for BMI, smoking status,

education, hypertension, diabetes, cholesterol, and family history of stroke. Hypertension was defined as systolic blood pressure greater than or equal to 140 mm Hg, or diastolic blood pressure greater than or equal to 90 mm Hg, or taking blood pressure medications, or any combination of these. We also used estimated cardiorespiratory fitness as a continuous variable via metabolic equivalent of task (MET; 1 MET was defined as 3·5 ml/kg/min) and estimated the difference between METs in HUNT1 and HUNT2 to assess the association between change in METs and dementia.

In a separate analysis, we used Laplace regression[27,28] adjusted for sex to estimate the years of life gained as the difference in survival years associated with the four different estimated cardiorespiratory fitness change groups. Reverse causality can be a problem in observational studies when the exposure–disease process is reversed. In preclinical years, dementia can affect risk factors and the association of these risk factors can be reversed when the follow-up is short.[29] We therefore did sensitivity analyses to test for reverse causality by excluding the first 3 years of follow-up for dementia incidence and the first 5 years for dementia mortality.

All statistical tests were two-sided, and p<0·05 was considered statistically significant. We used Stata statistical software (version 15.1; StataCorp, College Station, TX, USA) for all statistical analyses.

Role of the funding source

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

	Total	Unfit (≤20% eCRF)	Fit (>20% eCRF)	p value*
Participants, n	30 375	6622	23 753	..
Sex				
Male	14 450 (47·6%)	3115 (47·0%)	11 335 (47·7%)	..
Female	15 925 (52·4%)	3507 (53·0%)	12 418 (52·3%)	0·3270
Mean age, years (SD)	53·5 (13·1)	54·1 (15·5)	53·4 (12·3)	<0·0001
Mean eCRF, mL/kg/min (SD)	37·5 (8·1)	31·8 (7·7)	39·1 (7·4)	<0·0001
Mean eCRF, MET (SD)	10·7 (2·3)	9·1 (2·2)	11·2 (2·1)	<0·0001
Mean body-mass index, kg/m² (SD)†	26·6 (3·9)	30·2 (4·4)	25·6 (3·2)	<0·0001
High cholesterol‡				
Yes	3378 (11·1%)	924 (14·0%)	2454 (10·3%)	..
No	26 997 (88·9%)	5698 (86·0%)	21 299 (89·7%)	<0·0001
Diabetes status§				
Yes	897 (3·0%)	357 (5·4%)	540 (2·3%)	..
No	29 478 (97·0%)	6265 (94·6%)	23 213 (97·7%)	<0·0001
Smoking status				
Never	12 451 (41·0%)	2615 (39·5%)	9836 (41·4%)	..
Current	8540 (28·1%)	1861 (28·1%)	6679 (28·1%)	..
Former	9384 (30·9%)	2146 (32·4%)	8238 (30·5%)	0·0040
Years of education				
<10	12 522 (41·2%)	3246 (49·0%)	9276 (39·1%)	..
10–12	10 755 (35·4%)	2244 (33·9%)	8511 (35·8%)	..
>12	7098 (23·4%)	1132 (17·1%)	5966 (25·1%)	<0·0001
Hypertension status¶				
Yes	14 612 (48·1%)	4053 (61·2%)	10 559 (44·5%)	..
No	15 763 (51·9%)	2569 (38·8%)	13 194 (55·5%)	<0·0001
Family history of stroke				
Yes	6998 (23·0%)	1382 (20·9%)	5616 (23·6%)	..
No	23 377 (77·0%)	5240 (79·1%)	18 137 (76·4%)	<0·0001

Data are n (%) unless otherwise specified. eCRF=estimated cardiorespiratory fitness. MET=metabolic equivalent of task. *Baseline group differences were examined by using *t* test for continuous variables, and χ^2 tests were used for proportions of categorical variables. †Calculated as weight in kg divided by height in m². ‡Age-specific high cholesterol concentrations: >6·9 mmol/L for participants under 50 years, and >7·8 mmol/L for participants ≥50 years. §Diabetes was defined as non-fasting serum glucose concentration >11·1 mmol/L or reported history of diabetes. ¶Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mm Hg, or taking blood pressure medications.

Table 1: **Baseline characteristics of participants according to cardiorespiratory fitness levels**

Results

Between March 9, 1995, and July 14, 2010, 920 people were diagnosed with dementia. Of those, 44·6% were classified as having Alzheimer's disease, 17·7% as having vascular dementia, 12·6% as having mixed Alzheimer's disease and vascular dementia, 2·5% as having frontotemporal dementia, 4·5% as having dementia with Lewy bodies, and 18·1% as having other or unspecified dementia.[21] Of the 920 participants in the hospital HMS cohort, 703 participants had data in both the HMS and the HUNT study.[21] Of those, 383 were excluded from the analysis; 335 had missing data (on fitness, education, and smoking) and 48 self-reported myocardial infarction or history of stroke (figure 1). Excluded participants were older and had lower educational attainment than did those who were included in the study. 320 participants (182 women and 138 men) were included in our analysis on the association between cardiorespiratory fitness and incidence of dementia. In the dementia-related mortality cohort (n=30 375), 3341 (11%) participants reported taking blood pressure lowering drugs. Among these, 125 (4%) had systolic blood pressure below 120 mm Hg and 661 (20%) had systolic blood pressure between 120 and 139 mm Hg.

The mean age of participants at baseline was 53·5 years (SD 13·1) for those who were followed up for dementia mortality (table 1). Those who were followed up for incident cases of dementia had a mean age of 69·6 years (SD 8·2) at baseline. Participants with high estimated cardiorespiratory fitness were younger, more educated, had lower BMI, and a lower percentage had hypertension compared with those with low estimated cardiorespiratory fitness. The appendix (p 3) contains detailed baseline data according to estimated cardiorespiratory fitness in HUNT2.

The mean age of participants was 56·6 years (SD 14·1) for those who were unfit at both assessments, and 53·2 years (SD 12·6) for those who maintained high estimated cardiorespiratory fitness (table 2). Participants

who remained unfit at both assessments were less educated, weighed more, and had high prevalence of hypertension and diabetes compared with those who had sustained high estimated cardiorespiratory fitness at both timepoints.

Among 320 incident cases of dementia, the median follow-up was 7·6 years (IQR 5·3–9·5). An increase in estimated cardiorespiratory fitness, and sustained high estimated cardiorespiratory fitness over time, were associated with reduced risk of incident dementia (table 3). Compared with unfit participants with persistently low estimated cardiorespiratory fitness (in both HUNT1 and HUNT2), multi-adjusted analyses (adjusted for age, smoking status, BMI, diabetes status, education, hypertension, cholesterol, family history of stroke, and stratified by sex) showed that participants who had sustained high estimated cardiorespiratory fitness at both timepoints had a reduced risk of incident dementia (HR 0·60, 95% CI 0·36–0·99). For participants who increased their estimated cardiorespiratory fitness over time (unfit at HUNT1 and fit at HUNT2), the risk of incident dementia was also reduced (adjusted HR 0·52, 95% CI 0·30–0·90) compared with those who remained unfit at both assessments (table 3). In the analyses using change in estimated cardiorespiratory fitness as a continuous variable, each 1 MET increase over time was associated with risk reduction of incident dementia (adjusted HR 0·84, 95% CI 0·75–0·93; figure 2).

Compared with unfit participants at both assessments, those who increased their fitness levels over time (unfit at HUNT1 and fit at HUNT2) gained 2·2 (95% CI 1·0–3·5, p=0·01) dementia-free years. The corresponding dementia-free years for participants who were fit at both HUNT1 and HUNT2 were 1·1 (0·3–1·9, p=0·01; appendix p 4).

Of the 33 471 individuals who participated in both HUNT1 and HUNT2 and had cardiorespiratory fitness

	HUNT1 eCRF*: unfit		HUNT1 eCRF*: fit		p value†
	HUNT2 eCRF: uunfit	HUNT2 eCRF: fit	HUNT2 eCRF: unfit	HUNT2 eCRF: fit	
Participants, n	3025	3053	3597	20 700	..
Sex					
Male	1404 (46·4%)	1488 (48·7%)	1711 (47·6%)	9847 (47·6%)	..
Female	1621 (53·6%)	1565 (51·3%)	1886 (52·4%)	10 853 (52·4%)	0·3480
Mean age, years (SD)	56·6 (14·1)	54·9 (10·5)	52·1 916·4)	53·2 (12·6)	<0·0001
Mean eCRF, mL/kg/min (SD)	29·6 (7·1)	36·4 (6·8)	33·6 (7·7)	39·5 (7·4)	<0·0001
Mean eCRF, MET (SD)	8·5 (2·0)	10·4 (1·9)	9·6 (2·2)	11·3 (2·1)	<0·0001
Mean body-mass index, kg/m² (SD)‡	32·5 (4·4)	28·7 (3·3)	28·3 (3·3)	25·1 (2·8)	<0·0001
High cholesterol§					
Yes	434 (14·3%)	387 (12·7%)	490 (13·6%)	2067 (10·0%)	..
No	2591 (85·7%)	2666 (87·3%)	3107 (86·4%)	18 633 (90·0%)	<0·0001
Diabetes status¶					
Yes	246 (8·1%)	165 (5·4%)	111 (3·1%)	375 (1·8%)	..
No	2779 (91·9%)	2888 (94·6%)	3486 (96·9%)	20 325 (98·2%)	<0·0001
Smoking status					
Never	1187 (39·2%)	1138 (37·3%)	1428 (39·7%)	8698 (42·0%)	..
Current	815 (27·0%)	946 (31·0%)	1046 (29·1%)	5733 (27·7%)	..
Former	1023 (33·8%)	969 (31·7%)	1123 (31·2%)	6269 (30·3%)	<0·0001
Years of education					
<10	1670 (55·2%)	1465 (48·0%)	1576 (43·8%)	7811 (37·7%)	..
10–12	956 (31·6%)	1080 (35·4%)	1288 (35·8%)	7432 (35·9%)	..
>12	399 (13·2%)	508 (16·6%)	733 (20·4%)	5458 (26·4%)	<0·0001
Hypertension status‖					
Yes	2131 (70·4%)	1766 (57·8%)	1922 (53·4%)	8793 (42·5%)	..
No	894 (29·6%)	1287 (42·2%)	1675 (46·6%)	11 907 (57·5%)	<0·0001
Family history of stroke					
Yes	713 (23·6%)	788 (25·8%)	669 (18·6%)	4828 (23·3%)	..
No	2312 (76·4%)	2265 (74·2%)	2928 (81·4%)	15 87 (76·7%)	<0·0001

Data are n (%) unless otherwise specified. eCRF=estimated cardiorespiratory fitness. MET=metabolic equivalent of task. *Age-specific and sex-specific eCRF: unfit (≤20% of participants) and fit (>20% of participants). †For linear trend, we used regression analyses for continuous variables; we used χ^2 tests for proportions of categorical variables. ‡Calculated as weight in kg divided by height in m². §Age-specific high cholesterol levels: >6·9 mmol/L for participants aged <50 years, and >7·8 mmol/L for participants aged ≥50 years. ¶Diabetes was defined as non-fasting serum glucose levels of >11·1 mmol/L or reported history of diabetes, or both. ‖Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or taking blood pressure medications.

Table 2: **Characteristics of participants according to temporal changes in cardiorespiratory fitness levels**

	Dementia incidence		Dementia-related mortality	
	HUNT2 eCRF: unfit	HUNT2 eCRF: fit	HUNT2 eCRF: unfit	HUNT2 eCRF: fit
HUNT1 eCRF: unfit				
Events	32	34	83	74
HR (95% CI)	1 ref	0·52 (0·30–0·90)	1 ref	0·72 (0·52–0·99)
HUNT1 eCRF: fit				
Events	30	224	95	562
HR (95% CI)	0·84 (0·47–1·50)	0·60 (0·36–0·99)	0·77 (0·57–1·05)	0·56 (0·43–0·75)

HRs adjusted for age, smoking status, body-mass index, diabetes, education, hypertension, cholesterol, family history of stroke, and stratified by sex. eCRFs are age and sex specific: unfit (lower 20% of participants), and fit (upper 80% of participants). eCRF=estimated cardiorespiratory fitness. HR=hazard ratio.

Table 3: **HR of dementia incidence and mortality by changes in cardiorespiratory fitness**

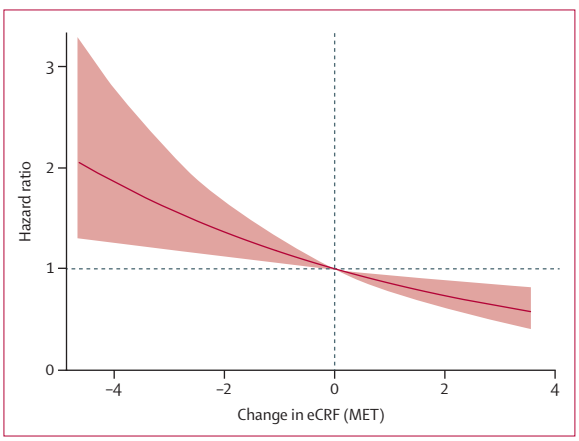

Figure 2: **Change in eCRF and dementia incidence**
Change in eCRF is expressed in METs; 1 MET was defined as 3·5 ml/kg/min. Solid line is hazard ratio and dotted lines are 95% CIs. Adjusted for age, body-mass index, smoking status, education, hypertension, diabetes, cholesterol, and family history of stroke, and stratified by sex. eCRF=estimated cardiorespiratory fitness. MET=metabolic equivalent of task.

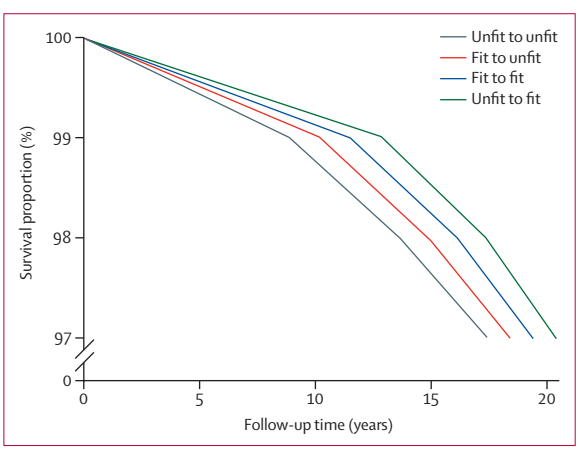

Figure 3: **Survival curves by change in eCRF for dementia-related mortality**
Participants were classified into two sex-specific eCRF groups according to their age (10-year categories): unfit (least fit 20%) and fit (most fit 80%). We used Laplace regression[28,29] adjusted for sex to estimate the years of life gained as the difference in survival years associated with the four different eCRF change groups. eCRF=estimated cardiorespiratory fitness.

data available, we excluded 3096 participants from mortality follow-up; 1897 owing to self-reported history of myocardial infarction or stroke and 1199 owing to missing data. 30 375 participants (15 925 women and 14 450 men) were included in our analyses of dementia mortality (figure 1). During the median follow-up of 19·6 years (IQR 19·1–20·2), there were 814 dementia-related deaths. An increase in estimated cardiorespiratory fitness (from unfit to fit) and sustained high estimated cardiorespiratory fitness over time were associated with reduced risk of dementia-related mortality (table 3). Compared with unfit participants at both HUNT1 and HUNT2, multi-adjusted analyses showed that participants who had sustained high estimated cardiorespiratory fitness at both timepoints had a reduced risk of dementia-related mortality (adjusted HR 0·56, 95% CI 0·43–0·75). For participants who increased their estimated cardiorespiratory fitness over time (unfit at HUNT1 and fit at HUNT2), our analyses also showed a reduced risk of dementia-related mortality (adjusted HR 0·72, 95% CI 0·52–0·99).

We saw an age-related decline in estimated cardiorespiratory fitness by about 2 mL/kg/min from HUNT1 to HUNT2 in both sexes. Men who changed status from unfit to fit between HUNT1 and HUNT2 had a mean estimated cardiorespiratory fitness of about 39·5 mL/kg/min in HUNT1, and 41 mL/kg/min in HUNT2.

When adjusted for sex, participants deemed fit at both HUNT1 and HUNT2 had gained 2·0 (95% CI 0·2–3·5, p=0·03) years of life compared with participants who were unfit at both assessments (figure 3). For those who increased their fitness over time (unfit at HUNT1 and fit at HUNT2), the corresponding years gained were 2·7 (95% CI 0·4–5·8, p=0·01). For those who decreased their estimated cardiorespiratory fitness over time (fit at HUNT1 and unfit at HUNT2), had no statistically significant years of life gained or lost, compared with those who remained unfit at both timepoints. Participants who maintained high cardiorespiratory fitness over time had reduced risk of dementia compared with those participants who remained persistently unfit over time. Notably, participants who improved their cardiorespiratory fitness over time also saw a reduction in their risk of dementia (figure 4).

Adjusted for baseline age, sex, smoking, BMI, diabetes, education, hypertension, cholesterol, family history of stroke, and fitness level at HUNT1, each ml/kg/min increase in estimated cardiorespiratory fitness corresponded with a risk reduction in dementia-related mortality (adjusted HR 0·97, 95% CI 0·95–0·99). Each MET increase in cardiorespiratory fitness was associated with a risk reduction in dementia-related mortality (adjusted HR 0·90, 95% CI 0·84–0·97).

In the sensitivity analyses done to check for reverse causality, there were 308 incident dementia cases available for analyses after excluding 3 years. For dementia mortality, the available number of events for analyses

was 773 after excluding 5 years of follow-up. We found that these exclusions had no effect on the results (data not shown).

Mean estimated cardiorespiratory fitness values for unfit women were 29·5 ml/kg/min (SD 5·1) in HUNT1 and 29·3 ml/kg/min (6·4) in HUNT2; for fit women, these values were 36·2 ml/kg/min (4·9) in HUNT1 and 37·0 ml/kg/min (6·3) in HUNT2. Mean estimated cardiorespiratory fitness values for unfit men were 37·7 ml/kg/min (5·3) in HUNT1 and 37·6 ml/kg/min (6·9) in HUNT2; for fit men, these values were 46·1 ml/kg/min (6·2) in HUNT1 and 47·0 ml/kg/min (6·9) in HUNT2. The estimated cardiorespiratory fitness models were highly comparable with previously published non-exercise prediction algorithms, and the accuracy of our model is similar to that of other studies.[24,30,31]

Discussion

The findings of the present study showed that men and women with persistently high estimated cardiorespiratory fitness, or improvement in estimated cardiorespiratory fitness from unfit to fit had 40–50% reduced risk of incident dementia, 30–40% reduced risk of dementia-related mortality, 2·0 years delay in onset of dementia, and 2–3 years of life gained, when compared to persistently unfit individuals. We also showed that each MET increase in estimated cardiorespiratory fitness was associated with a 16% reduced risk of dementia incidence and a 10% reduced risk of dementia mortality, and the relative risk values in those moving from fit to unfit over time were similar to those in people who were persistently unfit.

To our knowledge, only one previous study[17] has evaluated changes in estimated cardiorespiratory fitness and risk of incidence dementia. Kulmala and colleagues[17] investigated the association between perceived physical fitness at midlife (mean 50 years old) and changes in perceived physical fitness over three decades in 3559 men and women who were healthy at baseline. Similar to their findings, our results show that low estimated cardiorespiratory fitness at midlife is associated with increased risk of dementia incidence and that a decline in estimated cardiorespiratory fitness is associated with an increased risk of developing dementia. However, in contrast to their findings, we saw that an increase in estimated cardiorespiratory fitness from unfit to fit status is associated with a risk reduction of dementia incidence. We also report that obtaining high estimated cardiorespiratory fitness was associated with delayed onset of dementia by 2·2 years. These findings could have broad clinical and financial implications. For example, the estimated mean age of dementia onset in the USA is 83·7 years,[32] and it has been suggested that a novel treatment strategy delaying the onset of Alzheimer's disease by 5 years in individuals older than 70 years would result in a decrease of about 40% in both prevalence and costs of Alzheimer's disease in 2050.[33]

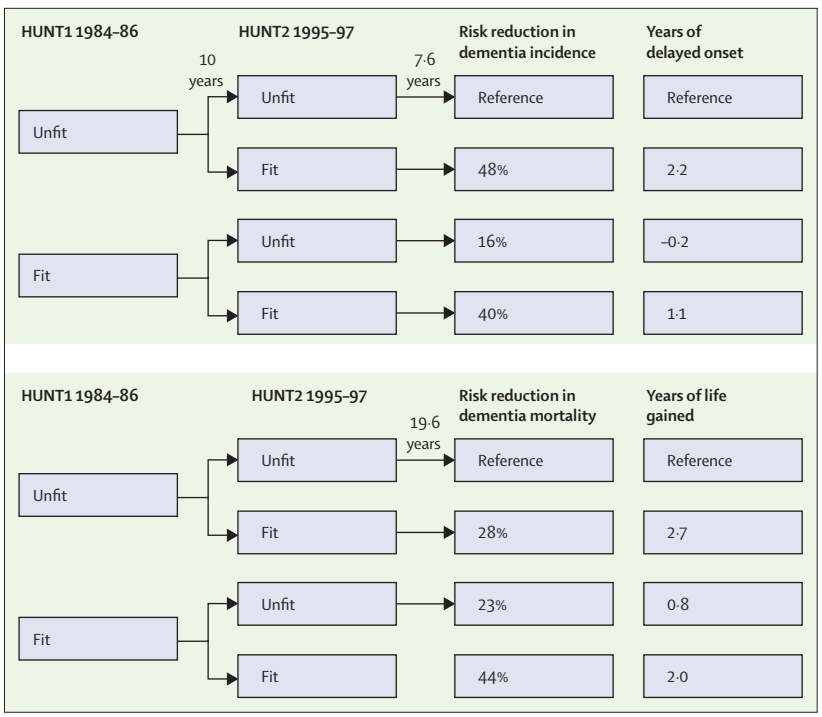

Figure 4: **Changes in eCRF relative to changes in incidence dementia, delayed onset of disease, dementia-related mortality, and life expectancy**

Participants were classified into two sex-specific eCRF groups according to their age (10-year categories): unfit (least fit 20%) and fit (most fit 80%). The follow-up time for incidence was 15·5 years, with a median of 7·6 years. The follow-up time for mortality was 21 years, with a median of 19·6 years. The analysis was adjusted for age, body-mass index, smoking status, education, hypertension, diabetes, cholesterol, and family history of stroke, and stratified by sex. eCRF=estimated cardiorespiratory fitness.

Although our study participants were about 10 years older than participants in Kulmala and colleagues' study[17] (aged 60 *vs* 50 years) when they entered the study, our data suggest that the association between estimated cardiorespiratory fitness and later risk of dementia is modifiable, also after midlife. We estimated cardiorespiratory fitness from a validated non-exercise prediction model,[24] whereas Kulmala and colleagues[17] assessed perceived estimated cardiorespiratory fitness by asking participants "how is your current physical fitness?", with possible answers ranging from very good to very poor. Although a decrease in perceived estimated cardiorespiratory fitness from midlife to later life was associated with an increased risk of dementia in Kulmala and colleagues' study,[17] it is not known whether that model of estimating cardiorespiratory fitness is sensitive in monitoring changes in cardiorespiratory fitness over time. This discrepancy could be attributed to differences at baseline or accuracy of cardiorespiratory fitness estimates between the two studies, or both. However, as the latter does not allow for estimation of cardiorespiratory fitness levels in mL/kg/min or METs, this theory remains speculative. Our findings that low estimated cardiorespiratory fitness might be a target for prevention even after midlife is supported by another longitudinal study[34] in

patients aged 77 years old with mild cognitive impairment. In this previous study,[34] those patients whose mild cognitive impairment converted into dementia within 7 years were less active than those whose mild cognitive impairment remained stable over time. Additionally, in individuals genetically predisposed to Alzheimer´s disease, a high estimated cardiorespiratory fitness can attenuate the increased risk of the disease, measured by examining biomarkers in cerebrospinal fluid.[35]

Previous prospective cohort studies[18,36] have shown a strong inverse association between estimated cardiorespiratory fitness and future risk of dementia-related mortality. However, the strong association seen between change in estimated cardiorespiratory fitness over time, reduced risk of dementia-related mortality, and more disease-free years in fit participants that eventually develop dementia is new. Considering that the median survival time after diagnosis is about 5 years for men and 7 years for women,[3] a prolongation of life by 2–3 years, as a result of maintaining or gaining high estimated cardiorespiratory fitness as observed in our study, is substantial. Whether or not patients have a less burdened disease course during this time is an important issue that warrants further investigation.

The beneficial effect of attaining a high estimated cardiorespiratory fitness on dementia disease course after diagnosis is debated.[37,38] A Cochrane review[39] concluded that despite no evidence of benefit of exercise on cognition, exercise programmes for people with dementia might improve their ability to do activities of daily living. The longer patients can stay independent, the greater the impact on the patient, patient's family, and society as a whole. A systematic review[40] with meta-analysis reported that physical exercise improved cognitive function in individuals aged 50 years and older, regardless of their cognitive status. The nature of our data prevents us from evaluating these factors and future studies are needed to elucidate this matter.

We observed an age-related decline in estimated cardiorespiratory fitness by about 2 mL/kg/min from HUNT1 to HUNT2 in both sexes, which is similar to a previous study.[41] Furthermore, men who changed status from unfit to fit between HUNT1 and HUNT2 had a mean estimated cardiorespiratory fitness of about 39·5 mL/kg/min in HUNT1, and 41 mL/kg/min in HUNT2. Counting in the observed age-related decline of 2 mL/kg/min from HUNT1 to HUNT2, a net increase in estimated cardiorespiratory fitness required to change from unfit to fit status in HUNT2 was about 3·5 mL/kg/min (ie, 1 MET). Notably, changing from unfit to fit between HUNT1 and HUNT2 implies a change that is achievable for most individuals. Our data suggest that physical activity recommendations should focus on activities with intensities that are proven to be effective in enhancing cardiorespiratory fitness.[42] Keeping the ageing population fit for longer could have huge positive public health and economic implications.[24] Population modelling studies[6] forecast that in the next 20 years, as more individuals will live to be older than 85 years, the population will face an increase in the number of individuals with complex multi-morbidity (at least four diseases; dementia being just one of them). Kingston and colleagues[6] state that health and social care services must adapt to these complex care needs,[5,6] and strongly advocate the need to focus on prevention of complex multi-morbidity. As low cardiorespiratory fitness has been associated with at least 26 chronic diseases,[8] including all diseases predicted to increase substantially up to year 2035 by Kingston and colleagues,[5] exercise training aiming to improve cardiorespiratory fitness could potentially be a key preventive strategy to avoid complex multi-morbidity. This strategy should be investigated further in future studies.

It is beyond the scope of this study to elucidate the mechanisms behind beneficial effects of having a high age-specific and sex-specific estimated cardiorespiratory fitness. However, the literature suggests that systemic neurotrophic factors are induced by exercise, and that these circulating biomolecules might cross the blood–brain barrier and be important to protect against neurodegenerative disorders, such as Alzheimer's disease.[43]

Several limitations of this study should be considered. First, the reported associations between estimated cardiorespiratory fitness and risk of dementia incidence and dementia-related mortality might not apply to all types of dementia, because we did not stratify dementia cases by dementia subtype. Second, although the HUNT study is one of the most comprehensive cohorts,[20] the sample size for incidence dementia was small, leading to a restricted statistical power for some of the analyses. Third, our study includes a relatively homogeneous sample of participants from Norway, which might limit the generalisability of the findings; however, the HUNT cohorts have been used in studies from other countries as a validation cohort to replicate their findings.[44] Fourth, not all of the people diagnosed with dementia during and after the observational period (1995–2010) have been identified,[21] which can also be considered as a strength as we do not overestimate the association between estimated cardiorespiratory fitness and dementia. Fifth, this study is an observational study and, as such, our findings are not causal. Sensitivity analyses were done to minimise the possibility of reverse causation, and we found no difference in our results when excluding those who were diagnosed up to 5 years after the start of follow-up. The lower participation rate in HUNT2 (about 70% attendance) than in HUNT1 (about 90% attendance) might have resulted in non-response bias. However, non-participation studies of non-responders after HUNT2 showed age-specific reasons for non-attendance.[20] For example, the main reasons for non-participation in people aged 20–44 years was lack of time and staying abroad; for people aged 70 years and older, the main reasons were having regular health check-ups or immobilisation due to

their conditions.[20] Galea and colleagues[45] argued that inherited study biases do not necessarily depend on low participation, and most epidemiological studies have found little evidence for substantial bias because of non-response. Finally, there was an insufficient number of events (thus statistical power) in the different estimated cardiorespiratory fitness change groups to allow for sex-specific results to be presented separately. Future studies with large enough event numbers are needed to help understand sex-specific findings of dementia and estimated cardiorespiratory fitness.

A main strength of the study is the data on change in estimated cardiorespiratory fitness in both men and women. The large number of individuals with dementia who participated in both HUNT1 and HUNT2 allows us to link individual dementia data with a vast amount of data collected in the HUNT database. Access to the detailed information on several potentially confounding factors gives us the opportunity to use predictive data collected three decades ago to study temporal changes and link to disease outcomes. Dementia incidence data were derived from the HMS, in which all participants had their dementia diagnosis confirmed by specialists in geriatric medicine and old-age psychiatry. The data on change in estimated cardiorespiratory fitness allow us to show that dementia risk is modifiable, and that one might decrease risk by attaining or sustaining a high estimated cardiorespiratory fitness.

Thus, maintaining a high cardiorespiratory fitness or improving cardiorespiratory fitness over time might be a target to reduce risk of developing dementia.

Contributors

ART, JN, UW, and NZ had full access to all 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, JN, and NZ collected the data. ART, JN, UW, and NZ analysed and interpreted the data. ART, JN, UW, HKS, IB, SB, GS, and NZ drafted the manuscript. ART, JN, UW, HKS, DS, IB, SB, GS, and NZ critically revised the manuscript. UW and JN supervised the study. ART and UW obtained funding.

Declaration of interests

We declare no competing interests.

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