





Joint impact of common risk factors on incident dementia: A cohort study of the Swedish Twin Registry

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Abstract. Tomata Y, Li X, Karlsson IK, Mosing MA, Pedersen NL, Hägg S (Karolinska Institute, Stockholm, Sweden; Tohoku University School of Public Health, Sendai, Japan; Jönköping University, Jönköping, Sweden; University of Melbourne, Melbourne, VIC, Australia). Joint impact of common risk factors on incident dementia: A cohort study of the Swedish Twin Registry. *J Intern Med*; 2020; **288**: 234–247.

Background. As common risk factors of dementia, nine factors (low education, hearing loss, obesity, hypertension, smoking, depression, physical inactivity, diabetes and social isolation) were proposed. However, the joint impact of these factors on incident dementia is still uncertain; hence, we aimed to examine this impact.

Methods. We conducted a cohort study of 9017 cognitively intact individuals aged ≥ 65 years in the Swedish Twin Registry. The main exposure was the total number of reported risk factors (ranging from 0 to 9). Data on dementia diagnoses were based on clinical workup and national health registers. After estimating the adjusted hazard ratios of incident dementia, the population attributable fraction (PAF) was calculated. We then

conducted additional analyses, including *APOE* $\epsilon 4$ status in a genotyped subsample ($n = 2810$) to check the relative impact of the main exposure and discordant twin pair ($n = 1158$) analysis to consider confounding by familial effects (shared genetic or familial environmental factors).

Results. The number of dementia cases was 1950 (21.6%). A dose-response relationship between the number of risk factors and incident dementia was observed; hazard ratio (95% confidence interval) per one-unit increment in number of risk factors was 1.07 (1.03 to 1.11). The PAF for the combination of the nine risk factors was 10.4%. The PAF of all nine risk factors was smaller than that of *APOE* $\epsilon 4$ genotype (20.8%) in the subsample. Discordant pair analysis suggested that the observed association was not likely explained by familial effects.

Conclusion. The nine risk factors may have considerable impact as modifiable factors on incident dementia.

Keywords: risk factors, dementia, cohort, joint effect, attributable fraction.

Background

Dementia is a worldwide public health problem, rapidly growing with population ageing [1]. In 2015, dementia affected 50 million people worldwide (about 5% of the world's older population aged ≥ 60 years), and it is estimated that the number will be 82 million by 2030 and 152 million in 2050 [2]. However, current medical treatments have only limited efficacy for treating dementia, and it is therefore important to clarify strategies aimed at primary prevention. Ecological observations have suggested a decline in age-specific dementia

incidence in several Western countries, and this population-level decrease may be explained by changes in educational level or lifestyles [3,4]. Thus, it was suggested that dementia is preventable by targeting modifiable risk factors. Because dementia is known to have a multifactorial aetiology, it is expected that a multidomain strategy targeted at several risk factors simultaneously would be effective [5]. Hence, it is important to establish the impact of modifiable risk factors on incident dementia.

More than 20 studies have examined the association between combinations of risk factors and

dementia [3,6-11]. One recent cohort study reported that an unfavourable lifestyle combination (current smoking, physical inactivity, unhealthy diet and alcohol consumption) was associated with a higher risk of incident dementia even after adjustment for genetic risk factors [6]. Additionally, one previous study of simulation based on literature data estimated that approximately 30% of dementia could be attributed to seven risk factors (low educational attainment, obesity, hypertension, physical inactivity, smoking, diabetes mellitus and depression); population attributable risks were estimated to be 28.2% worldwide, 30.6% in the United States, 31.4% in Europe and 30.0% in the UK [10]. Another cohort study also reported that 32.2% of incident dementia could be attributed to these seven risk factors [8].

Recently, the Lancet Commission proposed 'the Life-course model' that is based on a more comprehensive set of modifiable risk factors for dementia: (i) low education, (ii) hearing loss, (iii) obesity, (iv) hypertension, (v) smoking, (vi) depression, (vii) physical inactivity, (viii) diabetes and (ix) social isolation [3,10]. As much as 35% of dementia may be attributable to these modifiable risk factors, whereas 7% of dementia may be attributable to *APOE* ϵ 4 (a genetic and nonmodifiable risk factor) [3]. However, to our knowledge, no prospective study has yet investigated the joint impact of these nine risk factors on incident dementia.

Furthermore, most previous studies did not consider whether the association was explained by genetic liability of their study participants or early childhood exposure; hence, these findings may be confounded by familial effects (i.e. overestimation). Therefore, it is still uncertain whether the nine potential risk factors can be regarded as modifiable factors on incident dementia.

The aim of the present study was to examine the joint impact of all nine of the potential risk factors on incident dementia.

Methods

Study cohort

This cohort study included individuals who were part of the Screening Across the Lifespan Twin (SALT) study, aimed at all twins from the Swedish Twin Registry born 1958 or earlier [12]. Data collection through a computer-assisted telephone

interview was performed from March 1998 to December 2002. To obtain follow-up information on dementia, the SALT cohort was linked to national health registers using the personal identification number.

Figure 1 shows a flow chart of the study participants. Based on the 13 600 SALT participants who were ≥ 65 years at the time and completed the interview, exclusions were made for various reasons (Fig. 1). Thus, 9017 participants remained for the main analysis. The study participants comprised 4051 men (44.9%) and 4966 women (55.1%), with a mean (SD) age at the baseline of 72.1 (5.7) years.

To conduct the analysis including *APOE* ϵ 4 genotype, a subsample of 2810 persons who had genotype data was selected as 'Subsample I' (Figure 1) [13]. The subsample participants comprised 1393 men (49.6%) and 1417 women (50.4%), with a mean (SD) age at the baseline of 71.7 (5.8) years.

Furthermore, to conduct the analysis on changes in risk factors (exposure variables) across the life course, another subsample was created with 3063 persons born 1926–1958 who also participated in the questionnaire assessment conducted in 1972–1973 (Q73) as 'Subsample II' (Figure S1) [12,13]. The subsample participants comprised 1452 men (45.5%) and 1739 women (54.5%), with a mean (SD) age at the SALT baseline of 68.4 (2.5) years (age range: 65–74 years).

Dementia assessment

The primary outcome was incident dementia diagnosis retrieved from four kinds of data: (i) clinical dementia diagnoses data evaluated in the Swedish Twin Registry studies as described in previous reports [14,15]; (ii) the National Patient Register, which included both inpatient and outpatient records nationwide; (iii) the Cause of Death Register, which included death dates and causes; and (iv) the Prescription Drug Register, which included prescription for dementia medication (used as proxy for dementia diagnosis). This certification procedure has been used as a measure of incident dementia in previous studies [15-18].

For a dementia ascertainment, initial screening was conducted by the Mini-Mental State Examination or a telephone assessment for dementia (TELE) [19,20]. For all studies, a diagnostic consensus

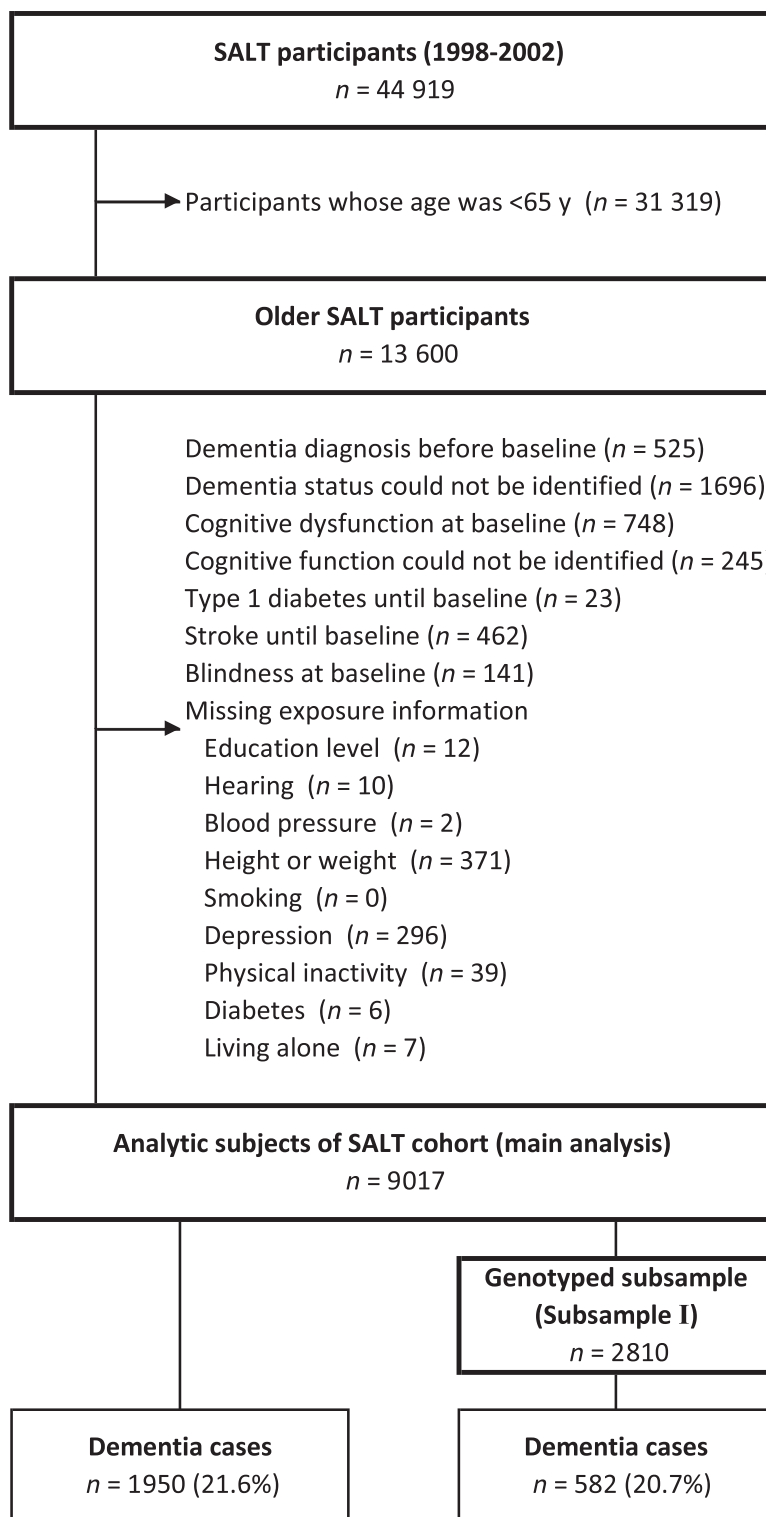


Fig. 1 Flow chart of the study participants.

board assigned a consensus clinical diagnosis using information from the in-person workup and medical records using DSM-III-R and DSM-IV criteria for dementia [15].

In addition, dementia information was retrieved through linkage of the national registry data from the Swedish National Patient Register, the Cause of Death Register and the Prescription Drug Register.

Participants were followed up from SALT baseline (1998–2002) until the date of dementia diagnosis, death or the end of the study period on 31 December 2016.

Exposures

The following nine self-reported risk factors were used as exposure variables: (i) low education, (ii) hearing loss, (iii) obesity, (iv) hypertension, (v) smoking, (vi) depression, (vii) physical inactivity, (viii) diabetes and (ix) living alone. These factors were included in the Lancet Commission's model [3], although we used living alone as a surrogate factor for social isolation due to lack of available data. Living alone has also been shown to be a risk factor for dementia in previous studies [21]. Table S1 shows definitions of dichotomous variables (having risk or not) for the nine risk factors. The total number of risk factors was summed, and participants were categorized into six groups according to the total number of risk factors (0, 1, 2, 3, 4 and ≥ 5 risk factors).

Because the Life-course model of the Lancet Commission included three exposures (hearing loss, obesity and hypertension) in middle age, in the additional analysis using Subsample II, we included information as follows: low education in early life (collected in the SALT study); hearing loss and obesity in middle age (collected in the Q73 study); and hypertension, smoking, depression, physical inactivity, social isolation and diabetes in older age (collected in the SALT study). Although the Life-course model includes midlife hypertension, we used data of hypertension in older age due to lack of available data. Table S2 shows differences in the definition of variables according to the Life-course model. Furthermore, amongst these nine risk factors, we could generate four exposure indicators of change in hearing loss, obesity, smoking and physical inactivity from Q73 (1972–1973) to SALT (1998–2002) in Subsample II

(Figure S6). Definitions of these risk factors are shown in Table S1.

Lists of detailed questions (variable information) for the SALT study or the Q73 study can be found at <https://ki.se/en/research/swedish-twin-registry-for-researchers>.

As a genetic risk factor, we used *APOE* $\epsilon 4$ genotype in the Subsample I analysis. *APOE* $\epsilon 4$ was directly genotyped or genotyped using Illumina OmniExpress and imputed against the 1000 Genomes Project phase 1 version 3 reference panel. Carriers of $\epsilon 2/\epsilon 4$ or $\epsilon 3/\epsilon 4$ were grouped as 'heterozygous', carriers of $\epsilon 4/\epsilon 4$ were grouped as 'homozygous', and other persons were grouped as 'noncarrier'.

Covariates

Baseline cognitive screening in the SALT study was conducted via a telephone assessment for dementia (TELE) [20]. The TELE includes questions about health and daily functioning, a 10-item mental status questionnaire, 3-word recall, serial 3s and a word similarity task (3 pairs). Participants received a TELE score ranging from 0 to 19.

If the participant performed poorly on the TELE (TELE score < 13.5), an informant was further interviewed with the Blessed Dementia Rating Scale (BDRS) [20,22]. The TELE and the BDRS were combined to classify four levels of cognitive status: 0, no cognitive dysfunction; 1, minor errors; 2, poor cognitive performance but no confirmation of interference with daily functioning; and 3, cognitive dysfunction [23]. A flow chart of the cognitive screening is shown in Figure S2. Although we excluded participants who were categorized with cognitive dysfunction at baseline, we applied the TELE score as a covariate (adjustment item) for level of baseline cognitive function for all remaining participants.

Statistical analyses

As main analyses, we used the multiple adjusted Cox model to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident dementia according to exposure variables (the number of risk factors and each of the nine risk factors). Age was used as the underlying timescale of follow-up. To consider the possibility that age, sex and cognitive function at baseline might affect the association between the number of risk factors and incident dementia, multivariate models were

adjusted for the following variables: age (continuous value), sex and cognitive function score (TELE score). We also generated a graph using the R packages 'coxph' and 'simGG' for the number of risk factors. To consider the influence of excluding 743 persons who had missing data for any of the nine risk factors, as a sensitivity analysis, we conducted multiple imputation for the nine risk factors using the SAS command 'PROC MI' [24]. We excluded 70 persons who had $\geq 20\%$ missing values for the nine risk factors, and we therefore included 9690 persons for the multiple imputation. We imputed missing values in each of the nine risk factors by the Markov chain Monte Carlo method (single chain) under the assumption of missing at random, and we applied the rounding strategy for binary data [25]. When a certain item of the nine risk factors was imputed, age and sex were also included as predictors. We conducted 20 imputations and then calculated pooled adjusted HRs (95% CIs) using analysis of the number of risk factors.

Population attributable fractions (PAFs) and 95% CIs were estimated based on the multivariate model using the Stata command 'PUNAF' [26].

Furthermore, we conducted three kinds of additional analyses. First, to consider the relative impact of the number of risk factors and *APOE* $\epsilon 4$ genotype, we conducted the analysis including *APOE* $\epsilon 4$ genotype in Subsample I ($n = 2810$) using the multiple adjusted Cox model.

Secondly, to consider whether familial effects (genetic factors or familial environmental factors) explained the association between the number of risk factors and incident dementia, we applied discordant twin pair analysis (within-pair analysis), that is co-twin matched case-control approach (selecting time-matched controls within twin pairs) for dementia-discordant twin pairs (participants whose dementia occurred first were defined as cases, and their co-twins were defined as controls) from 9017 SALT participants. Because some of these risk factors are, at least to some degree, explained by genetic factors [12–14], familial effects should be considered to test whether these risk factors are indeed modifiable. The flow chart for selecting dementia-discordant twin pairs is shown in Figure S3 (n of all discordant pairs = 1158; n of same-sex twin pairs = 770). In these analyses, only complete twin pairs were included and were stratified by zygosity into monozygotic (MZ) or dizygotic (DZ) pairs. MZ twins arise from a single zygote and

inherit identical genomic sequences, whereas DZ twins arise from two different zygotes and share on average 50% of their segregating genes. Additionally, shared familial environmental factors are assumed for both the MZ and DZ twin pairs. Therefore, if the association becomes attenuated in co-twin matched case-control analyses, familial effects are likely to contribute to the association [12]. In contrast, if a significant association remains when using co-twin matched pairs, the influences of familial effects on the association are likely to be marginal [12]. In addition, if genetic factors play a role, the association should be different between DZ and MZ pairs [12]. Conditional logistic regression models with family identification (twin pair identification) as the stratum variable were conducted for estimating adjusted odds ratios (ORs). As a sensitivity analysis of the discordant twin pair analysis, we also checked the results using conditional Cox models when we restricted data to 868 discordant twin pairs of incident dementia throughout the follow-up period (i.e. excluding 290 pairs where both twins developed dementia at different time during the follow-up).

Thirdly, to consider the life-course approach (difference of time to expose in middle age and older age), we conducted the analysis on the associations between changes in individual risk factors from middle age to older age and late-life incident dementia in Subsample II ($n = 3063$). This analysis was also done using the multiple adjusted Cox model for follow-up data from the SALT baseline.

Proportional hazards assumption was checked based on the Schoenfeld residual test using Stata command 'estat'.

We performed the analyses using SAS version 9.4 (SAS Inc., Cary, NC), STATA version 15 or R version 3.5.2. We considered two-sided P -values < 0.05 as statistically significant.

Ethical considerations

Data collection procedures were reviewed and approved by the Regional Ethics Board at Karolinska Institutet.

Results

Characteristics of study participants

Of the 9017 persons (115 541 person-years) included in the main analysis, 1950 persons

(21.6%) developed incident dementia. Data sources used for dementia diagnoses (1950 dementia cases) are shown in Table S3.

The baseline characteristics of participants according to the number of risk factors are summarized in Table 1. Individuals with a higher total number of risk factors were more likely to be older, to have slightly lower baseline cognitive function and to be women. The age- and sex-specific baseline characteristics are shown in Tables S4–S7.

The distribution of the number of risk factors is shown in Table S8. The mean (standard deviation) of the number of risk factors was 1.93 (1.26), and the range was 0–8 (no participant had 9 risk factors).

Joint impact

The main results of the present study are shown in Table 2. A dose-response relationship between the total number of risk factors and incident dementia was observed (P -trend < 0.001). HR (95% CI) of 1-unit increase (i.e. per 1 increment in the number of risk factors) was 1.07 (1.03 to 1.11) in the multiple adjusted model (P < 0.001). In this analysis (the HR of 1-unit increase), proportional hazards assumption was not rejected with the Schoenfeld residual

test (P = 0.279). Estimated HR of the number of risk factors on incident dementia in the multiple adjusted model is also shown in Fig. 2.

We also obtained similar results even when the multiple imputation method was applied (Table S9); the HR (95% CI) of 1-unit increase (i.e. per 1 increment in the number of risk factors) was 1.06 (1.02 to 1.10) in the multiple adjusted model (P = 0.002).

To examine possible reverse causality for the association, we re-analysed the association after excluding 57 participants who developed incident dementia in the first three years of follow-up, but the results for the number of risk factors did not change substantially; the HR (95% CI) of 1-unit increase was 1.07 (1.03 to 1.11) in the multiple adjusted model (P < 0.001).

The association did not differ significantly between age groups or sexes (Figure S4).

The PAF (95% CI) for the combination of the risk factors was 10.4% (–2.3 to 21.5%) (Table 2). PAFs (95% CI) of each category from 1 to ≥ 5 risk factors were as follows: 1.3% (–3.2 to 5.7%), 3.8% (–0.8 to 8.3%), 2.9% (–0.1 to 5.9%), 1.6% (0.0 to 3.0%) and 1.0% (0.2 to 1.7%), respectively.

Table 1. Characteristics at the baseline survey of the SALT study (1998 to 2002) according to number of risk factors (n = 9017)

	Total	Number of the risk factors					
		0	1	2	3	4	≥ 5
<i>n</i>	9017	1031	2555	2763	1673	718	277
Men (%)	44.9	51.5	48.9	44.2	41.1	36.6	36.1
Age (y) ^a	72.1 \pm 5.7	70.7 \pm 5.0	71.5 \pm 5.3	72.2 \pm 5.8	72.9 \pm 5.9	73.8 \pm 6.1	73.2 \pm 6.3
Cognitive function score ^{a,b}	16.3 \pm 1.6	16.6 \pm 1.5	16.4 \pm 1.6	16.2 \pm 1.7	16.2 \pm 1.7	16.1 \pm 1.6	16.1 \pm 1.6
Risk factors (%)							
(1) Low education	52.6	0	39.8	60.1	73.8	81.8	87.0
(2) Hearing loss	8.3	0	2.5	6.5	13.7	26.7	28.5
(3) Hypertension	31.4	0	12.3	33.4	53.1	66.4	82.7
(4) Obesity	8.3	0	1.3	5.4	14.1	26.0	50.2
(5) Smoking	29.5	0	19.1	32.7	43.4	52.0	60.7
(6) Depression	11.8	0	4.9	10.9	19.4	25.4	46.2
(7) Physical inactivity	10.0	0	2.0	7.9	16.1	31.2	49.5
(8) Diabetes	8.3	0	2.3	5.3	13.8	24.2	49.1
(9) Living alone	33.4	0	15.8	37.8	52.6	66.3	75.5

^aMean \pm SD (all such values).

^bTELE score (ranging from 0 to 19 points). A higher value means a better cognitive function.

Table 2. Association between number of risk factors and incident dementia ($n = 9017$)

	Number of risk factors ^a						P-	
	0	1	2	3	4	≥5	trend	PAF (%) ^f
<i>n</i>	1031	2555	2763	1673	718	277		
Event, <i>n</i>	210	550	608	376	148	58		
Event rate ^b	14.2	15.9	17.4	18.4	19.3	19.8		
Model 1 ^c	1.00 (reference) ^c	1.09 (0.93, 1.27)	1.23 (1.05, 1.44)	1.26 (1.06, 1.49)	1.37 (1.11, 1.70)	1.53 (1.14, 2.05)	<0.001	14.7% (3.0, 25.0%)
Model 2 ^d	1.00 (reference)	1.05 (0.90, 1.23)	1.14 (0.97, 1.33)	1.18 (1.00, 1.40)	1.26 (1.02, 1.56)	1.48 (1.11, 1.99)	<0.001	10.4% (-2.3, 21.5%)

^aRisk factors at the baseline survey of the SALT study (1998 to 2002) were the 9 items listed in Table 1.

^bNumber of incident dementia/1000 person-years.

^cAdjusted for age (continuous value) and sex.

^dAdjusted for Model 1 + cognitive function score (TELE) as continuous value.

^eHazard ratios (95% confidence interval) (all such values).

^fPopulation attributable fraction (PAF) if all participants would have adhered to the lowest group (number of risk factors = 0).

Individual risk factors and incident dementia

The associations between each of the nine risk factors and incident dementia, along with HRs and associated 95% CIs, are shown in Table 3. HRs of all risk factors were above 1. Hearing loss and diabetes displayed the higher HRs and were statistically significantly associated with a higher risk of incident dementia.

Additional analysis including APOE genotype

The impacts of the nine risk factors and APOE $\epsilon 4$ on incident dementia in Subsample I ($n = 2810$) are shown in Table 4. The tendency of a dose-response relationship of the nine risk factors was observed (P -trend = 0.093), and the PAF (95% CI) was 9.1% (-11.1 to 25.7%). This association did not differ significantly between APOE $\epsilon 4$ genotype groups (Figure S4). When we added APOE $\epsilon 4$ genotype to the model as an adjustment item, the PAF (95% CI) for the combination of the risk factors was 7.2% (-13.7 to 24.2%). The PAF (95% CI) of APOE $\epsilon 4$ genotype alone was 20.8% (15.5 to 25.8%).

Discordant twin pair analysis

The results of within-pair analyses in discordant twin pairs are shown in Fig. 3. The point estimates did not substantially attenuate within twin pairs ($OR_{\text{all pairs}} = 1.072$ and $OR_{\text{MZ}} = 1.124$), although 95% confidence intervals of these within-pair

estimates were wider than those of the main analysis due to smaller sample size. The OR in MZ twin pairs did not significantly differ from that of same-sex DZ twin pairs (1.124 vs. 1.047, P -interaction = 0.646).

Restricting the analysis to only 868 twin pairs who were discordant for incident dementia throughout the follow-up period did not change the results substantially (Figure S5).

Life-course exposures from middle age to older age

The associations between the total number of risk factors including data in middle age and incident dementia in Subsample II ($n = 3063$) are shown in Table 5. The total number of risk factors including data in middle age was also significantly associated with a higher risk of incident dementia (P -trend = 0.024). HR (95% CI) of 1-unit increase (i.e. per 1 increment of the risk factor number) was 1.09 (1.02 to 1.16) in the multiple adjusted model ($P = 0.016$). The PAF (95% CI) for the combination of the risk factors was 12.6% (95% CI: -7.8 to 29.1%). The nine risk factors based on data collected only in older age were also significantly associated with a higher risk of incident dementia (P -trend = 0.003; Table 5).

The associations between changes in risk factors from middle age to older age and late-life incident dementia using Subsample II ($n = 3063$) are shown

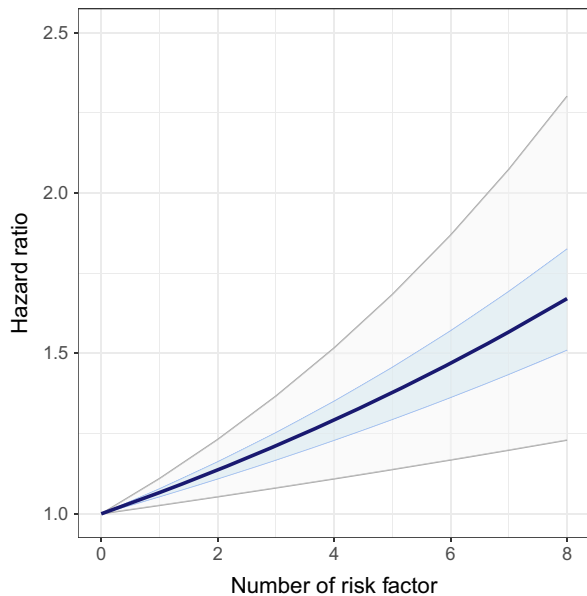


Fig. 2 Estimated hazard ratio of incident dementia according to the total number of the nine risk factors (low education, hearing loss, hypertension, obesity, smoking, depression, physical inactivity, diabetes and living alone) ($n = 9017$ older participants of the SALT study). The line represents point estimates of the hazard ratio, and error bands represent the smoothed 95% confidence interval (wider band) or 50% confidence interval (narrower band). This graph shows that participants who had a greater number of risk factors had a higher risk of incident dementia in a dose-dependent manner.

in Table 6. The concept of this analysis is illustrated in Figure S6. In comparison with the participants who were not obese at either middle age or

older age ('No & No' group), HR for participants who were obese in both middle age and older age ('Yes & Yes' group) was significantly higher. In comparison with the participants who were categorized as nonsmokers in both middle age and older age ('No & No' group), HR for the group who smoked in middle age ('Yes' group) tended to be higher, and the difference was not significant marginally. Although HR in the group of physical inactivity in both middle age and older age ('Yes & Yes' group) tended to be higher, the difference was not significant.

Discussion

In this cohort study, we investigated the impact of nine potential risk factors proposed by the Lancet Commission on incident dementia in an older Swedish population. As a result, we observed a statistically significant dose-response association between the number of risk factors and risk of incident dementia. This association did not change after adjusting for *APOE* $\epsilon 4$ genotype and stratifying by *APOE* $\epsilon 4$ genotype groups. Although we also considered the effects of reverse causality, the association between the number of risk factors and incident dementia persisted even after excluding individuals who developed dementia in the first three years of follow-up. HRs in analyses using each of the nine risk factors individually were higher than 1, although we observed statistically significant associations only for hearing loss and diabetes. Furthermore, point estimates from the discordant twin pair analysis implied that this association was not likely explained by familial effects (genetic factors or familial environmental

Table 3. Association between each risk factors and incident dementia ($n = 9017$)

Risk factors ^b	Prevalence, %	Hazard ratios ^a	
		No	Yes (having risk)
(1) Low education	52.6	1.00 (reference) ^b	1.03 (0.94, 1.12)
(2) Hearing loss	8.3	1.00 (reference)	1.29 (1.11, 1.50)
(3) Hypertension	31.4	1.00 (reference)	1.05 (0.95, 1.15)
(4) Obesity	8.3	1.00 (reference)	1.08 (0.92, 1.28)
(5) Smoking	29.5	1.00 (reference)	1.07 (0.96, 1.18)
(6) Depression	11.8	1.00 (reference)	1.04 (0.90, 1.20)
(7) Physical inactivity	10.0	1.00 (reference)	1.06 (0.90, 1.24)
(8) Diabetes	8.3	1.00 (reference)	1.33 (1.13, 1.56)
(9) Living alone	33.4	1.00 (reference)	1.06 (0.96, 1.17)

^aAdjusted for age (continuous value), sex and cognitive function score; TELE score (continuous value).

^bRisk factors at the baseline survey of the SALT study (1998 to 2002) were the 9 items listed in Table 1.

Table 4. Impacts of number of risk factors and APOE genotype on incident dementia (Subsample I: n = 2810)

	Prevalence, %	Event, n	Hazard ratios ^a	PAF (%)
Number of risk factors ^b				
0	15.1	84	1.00 (reference)	9.1% (-11.1, 25.7%)
1	30.3	170	1.03 (0.80, 1.34)	
2	29.6	174	1.11 (0.86, 1.45)	
3	16.7	104	1.19 (0.89, 1.59)	
4	6.2	38	1.26 (0.85, 1.86)	
≥5	2.1	12	1.28 (0.70, 2.35)	
APOE ε4 alleles ^c				
Noncarrier	72.1	343	1.00 (reference)	20.8% (15.5, 25.8%)
Heterozygous (ε2/ε4 or ε3/ε4)	25.9	216	1.93 (1.63, 2.29)	
Homozygous (ε4/ε4)	2.0	23	3.97 (2.60, 6.07)	

^aAdjusted for age (continuous value), sex and cognitive function score; TELE score (continuous value).

^bRisk factors at the baseline survey of the SALT study (1998 to 2002) were the 9 items listed in Table 1.

^cApolipoprotein E ε4.

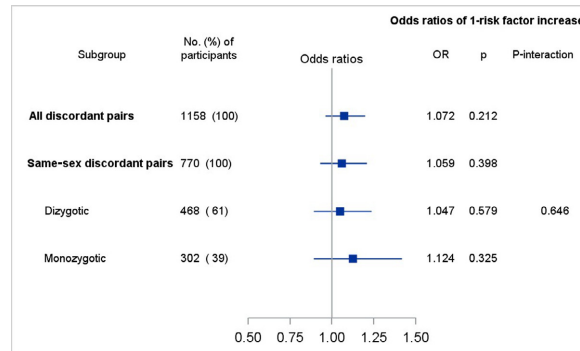


Fig. 3 Discordant twin pair analysis for the association between number of risk factors and incident dementia using conditional logistic regression. All dementia-discordant pairs (n = 1158) and same-sex dementia-discordant twin pairs (n = 770) from older participants of the SALT study were included.

factors). Therefore, these nine risk factors may be assumed to be modifiable risk factors on incident dementia.

However, the PAF of the nine risk factors in the present study (10.4%), and even the upper limit of the 95% CI (21.5%), was smaller than the PAF proposed in the previous report by the Lancet Commission (35%) [3]. Additionally, the PAF of all nine risk factors was relatively smaller than that of APOE ε4 genotype alone (20.8%). Therefore, the preventable fraction of these nine risk factors may not be as big as previously expected [27]. For PAF calculation based on a simulation approach using

literature data, such as the previous report by the Lancet Commission, communality of exposures (dependent risk factors) was suggested as a major limitation [10]. For example, the metabolic syndrome including three risk factors (diabetes, hypertension and obesity) is associated with physical inactivity, and all of these risk factors are associated with educational level [10]. If risk factors are not independent from each other, the combined PAF of the individual risk factors would be an overestimation [10]. On the other hand, original cohort studies (individual-level data) do not have this limitation because a cohort study can directly consider communality of exposures by using the

Table 5. Association between number of risk factors and incident dementia (Subsample II: n = 3063)

	Number of risk factors						P-trend	PAF (%) ^e
	0	1	2	3	4	≥5		
Nine risk factors along with the Life-course model: Risk factors in middle age or older age were included ^a								
n	421	925	932	542	178	65		
Event, n	75	164	190	108	29	17		
Model 1 ^b	1.00 (reference) ^d	1.04 (0.79, 1.37)	1.30 (0.99, 1.70)	1.30 (0.97, 1.75)	1.19 (0.77, 1.82)	2.00 (1.18, 3.38)	0.005	15.1% (-4.6, 31.0%)
Model 2 ^c	1.00 (reference)	1.03 (0.78, 1.35)	1.26 (0.96, 1.64)	1.24 (0.93, 1.67)	1.08 (0.70, 1.66)	1.82 (1.07, 3.10)	0.024	12.6% (-7.8, 29.1%)
Nine risk factors including only later-life risk factors except low education ^f								
n	441	914	921	504	211	72		
Event, n	77	159	183	110	38	16		
Model 1 ^b	1.00 (reference) ^d	1.06 (0.81, 1.39)	1.33 (1.02, 1.74)	1.44 (1.08, 1.93)	1.47 (0.99, 2.17)	1.73 (1.01, 2.97)	<0.001	18.2% (-0.4, 33.4%)
Model 2 ^c	1.00 (reference)	1.05 (0.80, 1.38)	1.29 (0.99, 1.69)	1.39 (1.04, 1.87)	1.31 (0.89, 1.95)	1.58 (0.92, 2.71)	0.003	16.0% (-3.3, 31.6%)

^aLow education in early life; hearing loss and obesity in middle age (collected in Q73 [1973]); and hypertension, smoking, depression, physical inactivity, social isolation and diabetes in older age (collected in SALT [1998 to 2002]).

^bAdjusted for age (continuous value) and sex.

^cAdjusted for Model 1 + cognitive function score (TELE) as continuous value.

^dHazard ratios (95% confidence interval) (all such values).

^ePopulation attributable fraction (PAF) if all participants would have adhered to the lowest group (number of risk factors = 0).

^fRisk factors were the 9 items listed in Table 1 (the same exposure definition used in Table 2). Only SALT data (at the time when all samples were older age) were included.

number of risk factors as the exposure variable. In the present study, educational level was associated with the other risk factors (Table S10). Furthermore, the PAF of having 1 risk factor (1.3%) was smaller than that of having ≥ 2 risk factors (9.3%) in the present study. Therefore, the impact of the nine risk factors should be interpreted as mainly due to combinations of risk factors rather than each risk factor alone. However, because the PAF of an original cohort study depends on the profiles of the risk factors in the cohort data, the PAF of the present study may not be a representative result for other populations. Cohort studies typically include participants who are healthier, have higher social status and have less disease than the source population of interest [28]. Therefore, cohort studies may generally underestimate the PAF because the prevalence of the risk factors is lower than in the source population. However, because the PAF

of the *APOE* $\epsilon 4$ genotype in the present study was bigger than that previously reported [3], it is unclear whether all results in the present study are underestimated compared to the report by the Lancet Commission [3].

When information on hearing loss and obesity in middle age was included along with the Life-course model, we observed a significant association and 12.6% of the PAF (Table 5) in line with the main result (Table 2). However, in Subsample II ($n = 3063$), using the nine risk factors based on data only in older age (the same exposure data as the main analysis in Table 2) showed more robust associations with a higher risk of incident dementia (Table 5). Therefore, it was unclear whether we should focus on exposing hearing loss or obesity especially in middle age. Because data of risk factors in older age might include effects of long-

Table 6. Association between change in risk factors and incident dementia (Subsample II: n = 3063)

	Exposure in middle and older age ^a	n	Hazard ratios ^b
Hearing loss	No & No	2618	1.00 (reference)
	No & Yes	100	1.18 (0.77, 1.81)
	Yes & No/Yes	345	1.00 (0.77, 1.30)
Obesity	No & No	2775	1.00 (reference)
	No & Yes	203	1.07 (0.77, 1.49)
	Yes & No	25	1.28 (0.53, 3.10)
	Yes & Yes	60	1.84 (1.08, 3.13)
Smoking	No & No	1624	1.00 (reference)
	No & Yes	79	1.26 (0.77, 2.06)
	Yes & No/Yes	1360	1.18 (0.999, 1.40)
Physical inactivity	No & No	2636	1.00 (reference)
	No & Yes	156	1.39 (0.98, 1.97)
	Yes & No	220	0.94 (0.68, 1.29)
	Yes & Yes	51	1.35 (0.72, 2.53)

^aExposure in middle age (left side of 'Yes' or 'No') based on Q73 data (baseline survey in 1973). Exposure in older age (right side of 'Yes' or 'No') based on SALT data (baseline survey in 1998–2002). Age range at baseline in older age: 65–74 years. Because we assumed that effects of hearing loss or ever smoking in middle age persisted even in older age, we categorized them as 'Yes & No/Yes'.

^bHazard ratios of Model 2 in Table 2.

term exposure before baseline, we should consider about change in risk factors from middle age to older age.

In age-stratified analysis using the number of risk factors (Figure S4), the association in the younger age group (65–71 year [less than median age]) tended to be stronger than in the older age group (≥ 72 year [median age or more]). Additionally, in terms of exposing in risk factors from middle age to older age, obesity in both middle age and older age was significantly associated with a higher risk of incident dementia (but not obesity only in middle age). We also observed that cumulative exposure to smoking and physical inactivity tended to infer higher risk for incident dementia. Taken together, these results may support the hypothesis that long-term cumulative exposures of risk factors are more important for the prevention of late-life dementia, rather than prevention strategies only in

late life. Indeed, a previous study suggested that maintaining a higher level of physical activity from middle age to older age may be a preventive factor for dementia in older age [29]. Thus, from a life-course perspective, it may be debatable whether exposure to these risk factors only in middle age or only in older age is the preferred model on incident dementia, although the present findings supported that the combination of the nine kinds of risk factors would be a risk factor of incident dementia.

Although definitions of the nine risk factors in the present study were based on previous findings (especially the Lancet Commission's report [3]), as a sensitivity analysis, we changed the cut-off definition of low education (which had the lowest HR amongst the nine risk factors) from 'primary school graduation or less' to 'high school graduation or less'. As a result, the association between low education and incident dementia was more pronounced but still not statistically significant. The multivariate HR (95% CI) of low education (high school graduation or less) was 1.11 (0.96 to 1.28; data not shown). Therefore, a potential impact based on the theoretical-maximum risk exposure distributions of the nine risk factors on incident dementia remains unclear.

Our study had a number of strengths: (i) comparative impact of the nine risk factors and *APOE* $\epsilon 4$ genotype was evaluated, (ii) familial effects were considered by the twin pair design, (iii) changes in risk factors from middle age to older age were considered, and (iv) it was a relatively large cohort study (9017 persons).

This study had also several limitations. First, because data on all nine risk factors were based on self-reports, some misclassification of exposure variables might have occurred. For example, our hearing loss definition was not based on information from a hearing test using specialized calibrated equipment. If there had been considerable nondifferential misclassification, the present results (e.g. HRs) would have been underestimated [30]. Secondly, because we applied living alone instead of social isolation, our definition of exposures was not exactly the same as the definition from the Lancet Commission [3]. Additionally, we did not examine the change in the total number of nine risk factors from middle age to older age. Thirdly, our results may have been influenced by selection bias. The response rate was 65% amongst the eligible older twins (still alive and living in Sweden) who were

born in 1886 to 1925 [31]. Thus, it cannot be ruled out that our participants were biased towards healthier people. If so, underestimation of PAFs may have occurred because the prevalence of having the risk factors would have been lower than in our source population. In particular, our subsample populations (Subsample I and Subsample II) had significantly lower mean age and higher cognitive function score ($P < 0.01$; Table 1, Tables S11 and S12). Therefore, caution should be taken when interpreting the results using the subsamples, as they may not be a good representation of the original SALT population. Fourthly, we mainly detected cases of incident dementia by Swedish registry data; 47.0% of dementia cases came from either the Cause of Death Register or the National Patient Register (Table S3). Therefore, we could not rule out the possibility that our results were underestimated by nondifferential misclassification regarding dementia onset. Fifthly, the sample size may not have been sufficient, especially in the discordant twin pair analysis ($n = 1158$). Because the confidence interval of the PAF in the present study was not narrow (-2.3% to 21.5%), future studies based on larger sample sizes are needed for more precise estimation of the PAF.

In conclusion, the present study suggests that the combination of the nine common risk factors is associated with a higher risk of incident dementia and can be regarded as modifiable. Even if the present study underestimated the impact of the joint effect of the nine risk factors by the aforementioned limitations, the public health impact would be considerable in the context of population ageing. The findings of the present study imply the importance of a multidomain strategy targeting all the risk factors simultaneously for dementia prevention.

Acknowledgements

We would like to thank Juulia Jylhävä, Shu Zhang, Ge Bai, Xiaoying Kang and Ichiro Tsuji for their technical assistance.

Conflict of Interest

All other authors declare no competing interests.

Funding

This work was supported by the Swedish Council for Working Life and Social Research (FORTE)

(2013-2292), the Swedish Research Council (2015-03255), King Gustaf V's and Queen Victoria's Freemason Foundation, the Strategic Research Area in Epidemiology at Karolinska Institutet and the Leading Young Researcher Overseas Visit Program from Tohoku University, Japan. This was an investigator-initiated study. The sponsor and funders of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flowchart of the Subsample II.

Figure S2. Flowchart of the telephone cognitive screening.

Figure S3. Flowchart of the sample for the discordant twin pair analysis.

Figure S4. Stratified analysis: number of risk factors and incident dementia.

Figure S5. Discordant twin-pair analysis for the association between number of risk factors and incident dementia (conditional Cox models analysis using 868 twin pairs who were discordant for incident dementia throughout the follow-up period).

Figure S6. Concept of the analysis for the change in risk factors.

Table S1. Definition of nine risk factors.

Table S2. Differences in the definition of variables according to the Life course model.

Table S3. Data sources used for dementia diagnoses ($n = 1950$ dementia cases).

Table S4. Characteristics at the baseline survey of the SALT study (1998 to 2002) according to the number of risk factors: men aged <72 years ($n = 2211$).

Table S5. Characteristics at the baseline survey of the SALT study (1998 to 2002) according to the number of risk factors: men aged ≥ 72 years ($n = 1840$).

Table S6. Characteristics at the baseline survey of the SALT study (1998 to 2002) according to the number of risk factors: women aged <72 years ($n = 2533$).

Table S7. Characteristics at the baseline survey of the SALT study (1998 to 2002) according to the number of risk factors: women aged ≥ 72 years ($n = 2433$).

Table S8. Distribution of the number of risk factors ($n = 9017$).

Table S9. Association between number of risk factors and incident dementia (multiple imputation).

Table S10. Difference in frequency of risk factors related to low education ($n = 9017$).

Table S11. Characteristics at the baseline survey of the SALT study (1998 to 2002) according to number of risk factors: Subsample I ($n = 2810$).

Table S12. Characteristics at the baseline survey of the SALT study (1998 to 2002) according to number of risk factors: Subsample II ($n = 3063$).■