RESEARCH ARTICLE OPEN ACCESS

Low Values for Blood Pressure, BMI, and Non-HDL Cholesterol and the Risk of Late-Life Dementia

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Neurology® 2022;99:e1630-e1639. doi:10.1212/WNL.0000000000200954

Abstract

Background and Objectives

Low values of blood pressure, body mass index (BMI), and non–high-density lipoprotein (HDL) cholesterol have all been associated with increased dementia risk in late life, but whether these risk factors have an additive effect is unknown. This study assessed whether a combination of late-life low values for systolic blood pressure (SBP), BMI, and non-HDL cholesterol is associated with a higher dementia risk than individual low values of these risk factors.

Methods

This is a post hoc analysis based on an observational extended follow-up of the Prevention of Dementia by Intensive Vascular Care (preDIVA) trial, including community-dwelling individuals, aged 70–78 years and free from dementia at baseline. We assessed the association of baseline low values of SBP, BMI, and non-HDL cholesterol with incident dementia using Cox regression analyses. First, we assessed the respective associations between quintiles of each risk factor and dementia. Second, we explored whether combinations of low values for cardiovascular risk factors increased dementia risk, adjusted for interaction and potential confounders.

Results

During a median follow-up of 10.3 years (interquartile range 7.0–10.9 years), 308 of 2,789 participants (11.0%) developed dementia, and 793 (28.4%) died. For all risk factors, the lowest quintile was associated with the highest adjusted risk for dementia. Individuals with 1, 2, and 3 low values had adjusted HRs of 1.18 (95% CI 0.93–1.51), 1.28 (95% CI 0.85–1.93), and 4.02 (95% CI 2.04–7.93), respectively, compared with those without any low values. This effect was not driven by any specific combination of 2 risk factors and could not be explained by competing risk of death.

Discussion

Older individuals with low values for SBP, BMI, or non-HDL cholesterol have a higher dementia risk compared with individuals without any low values. Dementia risk was substantially higher in individuals with low values for all 3 risk factors than expected based on a dose-response relationship. This suggests the presence of an overarching phenomenon that involves multiple risk factors simultaneously, rather than resulting from independent effects of each individual risk factor.

Trial Registration Information

ISRCTN registry preDIVA: ISRCTN29711771. Date of study submission to ISRCTN registry: February 14, 2006. Recruitment start date: January 1, 2006. doi.org/10.1186/ISRCTN29711771.

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The Article Processing Charge was funded by the authors.

Glossary

AHM = antihypertensive medication; **BMI** = body mass index; **CLD** = cholesterol-lowering drug; **CVD** = cardiovascular disease; **GP** = general practitioner; **HDL** = high-density lipoprotein; **HR** = hazard ratio; **IQR** = interquartile range; **MMSE** = Mini-Mental State Examination; **POE** = preDIVA observational extension; **preDIVA** = Prevention of Dementia by Intensive Vascular Care; **SBP** = systolic blood pressure; **TC** = total cholesterol; **TICS** = telephone interview for cognitive status.

Cardiovascular risk factors including high blood pressure, obesity, and high cholesterol in midlife, commonly defined as 45–64 years, are important risk factors for dementia in late life (65 years and above).[1,2] However, in late life, low values for these risk factors have also been associated with increased dementia risk.[3-8]

The relationship between late-life systolic blood pressure (SBP) and incident dementia may be inverse or follow a U-shaped curve, with both high and low blood pressure values indicating an increased dementia risk.[9,10] U-shaped associations with dementia have been described for non–high-density lipoprotein (HDL) cholesterol levels[6] and inverse relations for late-life total cholesterol (TC) levels[4,5] and body mass index (BMI).[7,8]

Contrasting relationships have been described for a variety of (cardiovascular) risk factors and outcomes in older people, a term generally used to describe individuals aged >65 years.[11] Still, the exact nature of inverse or U-shaped associations and how they develop in late life remain unclear. For each of the risk factors above, different pathophysiologic mechanisms have been proposed.[6,12,13] However, because these relationships develop similarly with aging for several cardiovascular risk factors and have been observed for other adverse outcomes including cardiovascular disease (CVD) and all-cause mortality, these may reflect an overarching phenomenon involving all of these risk factors. Several overarching hypotheses have been proposed to explain these inverse or U-shaped relationships. First, survival bias might play a role, wherein the selection of individuals who survive to old age with high values of cardiovascular risk factors might be less susceptible to their potential harmful effects.[4] Second, contrasting associations in late life might reflect a state of impaired homeostasis across a range of physiologic processes and organ systems, possibly contributing to the development of dementia or indicating increased dementia risk by being a marker of physical aging beyond calendar years. Alternatively, the relationship may be retrocausal, with low values for risk factors being early signs of neurodegeneration. Previous research suggests that declining risk factor values over time may precede dementia diagnosis. If measured at 1 time point, it may therefore appear that individuals with low levels have the highest risk.[11,14-17] Finally, competing risk of death might play a role in these associations in older people, as similar contrasting relationships with cardiovascular risk factors have been observed for mortality.[11]

Better identification of older individuals at an increased risk of dementia is especially important in clinical practice where prevention guidelines are based on risk factors in midlife. Furthermore, if older individuals with low values for a combination of risk factors might explain the inconsistent associations reported in the literature, while positive linear associations are observed in younger groups, trials might (re) evaluate the efficacy of intensive treatment of risk factors in this subgroup.

In this study, we investigated the associations of low SBP, low BMI, and low non-HDL cholesterol with the risk of dementia and whether the combination of these factors signal increased risk beyond the sum of their individual associations. Furthermore, we assessed how these relationships are influenced by the competing risk of death.

Methods

Study Design and Participants

We used data from the Prevention of Dementia by Intensive Vascular Care (preDIVA) trial and the preDIVA observational extension (POE) study.[18,19] The preDIVA cluster randomized trial compared the effect of intensive vascular care, that is, 4-monthly visits to a practice nurse, comprising assessment of cardiovascular risk factors and tailored lifestyle advice, with care as usual on incident dementia after a median intervention and follow-up period of 6.7 years in 3,526 community-dwelling older adults (70–78 years). After an additional 3.6 years of observational extension in the POE study, information on dementia status and mortality was obtained of those participants who had not reached the primary end point or had not deceased during the preDIVA trial, resulting in information about dementia status in a total of 3,491 participants (99%). Study protocols and outcomes have been published in detail elsewhere.[18-20] Because there was no effect of the intervention, we considered the population as 1 cohort for the current study. This study is presented following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational cohort studies.[21]

Independent Outcome Variables

Data on demographics and other independent variables were collected at baseline. All variables were assessed using standardized devices and operating procedures. SBP was calculated using the mean of 2 measurements on the same arm, measured at least 5 minutes apart, performed with the electronic OMRON M6 device. Cholesterol levels were determined in local laboratories affiliated with the general practitioner (GP) practices. We computed non-HDL cholesterol levels for each participant by subtracting HDL cholesterol from TC values.

Self-reported data on medical history and medication use were crosschecked with GPs' electronic health records. The ApoE genotype was determined at a central laboratory in the Amsterdam University Medical Center, location AMC. Data on education and smoking were self-reported and defined in line with the World Health Organization criteria.[18]

Dementia Diagnosis

The adjudication process for the outcome dementia has previously been described in detail.[18] In short, a clinical dementia diagnosis was evaluated by an independent outcome adjudication committee, according to the *Diagnostic and Statistical Manual of Mental Disorders IV*.[22] Participants underwent regular assessments every 2 years and at the final assessment, during the 6–8 years trial phase of preDIVA. Individuals with cognitive complaints, a Mini-Mental State Examination (MMSE) score of ≤24, and a decline of ≥3 points from baseline MMSE or ≥2 points since the preceding 2-yearly visit were referred to their GP for clinical evaluation and adjudication by the outcome committee. All diagnoses were reevaluated after 1 year. In case of dropout, dementia status was retrieved from the GP or the electronic health records and evaluated by the adjudication committee.

For the observational extension, the telephone interview for cognitive status (TICS) was administered to all participants who were still alive and willing to participate, 3–4 years after the conclusion of the preDIVA trial.[23] Participants with a TICS score >30 and no formal dementia diagnosis were classified as not having dementia. In all other cases, the GPs' electronic health records were searched to verify whether a diagnosis of dementia had been made. All data pertaining to incident dementia diagnoses were subsequently evaluated for confirmation by the adjudication committee.

Statistical Analysis

We included all participants with available baseline data on SBP, BMI and non-HDL cholesterol, covariates, and outcome data of dementia. Descriptive variables were stratified by dementia diagnosis and presented using mean and SD when normally distributed. Non-normally distributed continuous variables were presented as median and interquartile range and categorical variables as frequencies and percentages.

All analyses were performed using Cox proportional hazards regression analysis. First, we assessed the association between each risk factor at baseline (SBP, BMI, and non-HDL cholesterol) divided in quintiles and dementia during follow-up. We used quintiles as independent variable because there is no consensus on the optimal values for cardiovascular risk factors in late life because current guidelines are based on risk prediction in midlife. Use of quintiles balances the advantage of sufficient data granularity with the loss of power due to small groups. Second, to assess the association between a combination of low values of these risk factors and incident dementia, we dichotomized the independent variables into low vs any higher values based on quintiles (lowest quintile vs all other quintiles). According to this dichotomization, each individual was assigned to 1 of 4 groups: (1) no low values, (2) 1 low value, (3) 2 low values, and (4) 3 low values. We included the number of low values as a categorical variable in our model, with no low values as the reference category. The p value for trend and the overall hazard ratio (HR) were calculated by including the number of low values as a numeric variable in the model. Third, interactions between low values of the risk factors on dementia incidence were assessed using interaction terms (low values of: SBP × non-HDL, non-HDL × BMI, and BMI × SBP). We used 3 models for each analysis. In model 1, age was used as timescale and age at baseline as time of study entry, without further adjustments. Model 2 was additionally adjusted for sex and educational level. Model 3 was additionally adjusted for smoking status, history of diabetes, stroke or CVD (angina pectoris, myocardial infarction, and/or peripheral artery disease), and *ApoE4* genotype. We assessed the proportional hazards assumption by visual inspection of Schoenfeld residuals.

Predefined subgroup analyses were performed for (1) sex, (2) ApoE4 genotype, (3) history of CVD, (4) antihypertensive medication (AHM) use vs no AHM use, and (5) cholesterol-lowering drug (CLD) use vs no CLD use because the associations might differ when risk factor values are low because of medication effects. We used the maximally adjusted model (model 3) for the subgroup analyses.

We performed several sensitivity analyses. First, we repeated the main analysis with low values based on clinical cutoff values instead of quintiles (i.e., SBP 140 mm Hg, BMI 25 kg/m^2, and non-HDL cholesterol 3.4 mmol/L) to compare our results with regard to current clinical practice. Second, we explored whether effects observed in our main analysis were driven by specific combinations of cardiovascular risk factors. Third, we performed analyses according to median time to dementia diagnosis to evaluate the influence of time between risk factor exposure and dementia onset. Low values for SBP, BMI, and non-HDL cholesterol might be prodromal factors developing with incipient dementia, in which case their association with increased dementia risk would be particularly strong in the short term.[14,15] Fourth, analyses according to randomization group were performed to investigate whether there were differential effects between the intervention and control group of the original preDIVA trial, although the trial results were neutral. Fifth, because mortality is an important competing risk for dementia, especially in cohorts of older people with relatively long follow-up which have substantial mortality rates, we performed sensitivity analyses to assess the competing risk of death in a cause-specific hazard approach, with mortality and the combined outcome dementia and mortality.[24] Sixth, we repeated the main analysis with data divided in tertiles rather than quintiles, increasing the number of cases in each group. Finally, to assess the effect of our specific choices for measures of cholesterol and blood pressure, we repeated the main analyses using different commonly used measures, including TC, LDL cholesterol, and HDL cholesterol (highest quintile) instead of non-HDL

cholesterol, and diastolic instead of systolic blood pressure. Analyses were conducted in RStudio (version 4.0.3).

Standard Protocol Approvals, Registrations, and Patient Consents

The ethics committee of the Amsterdam University Medical Center, location Academic Medical Center, approved both studies, and all individuals gave written informed consent.

Data Availability

All data used for this study are available from the authors on reasonable request.

Results

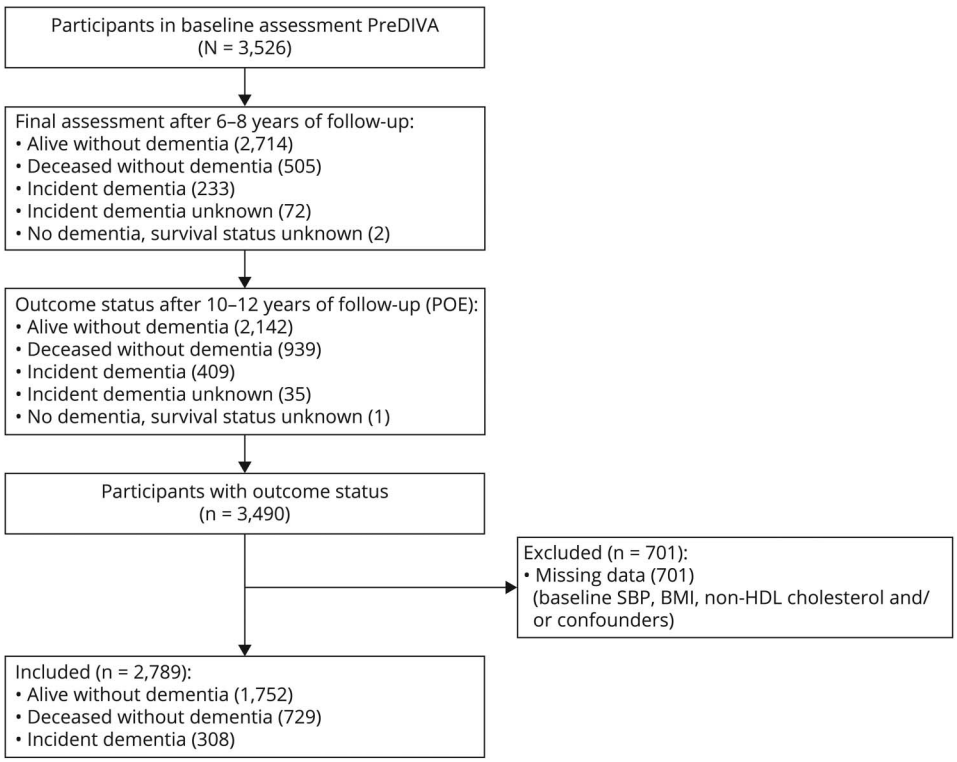
A total of 2,789 individuals with a median age of 74 years (interquartile range [IQR] 72–76 years) were included in this analysis (Figure 1). Over a median follow-up of 10.3 years (IQR 7.0–10.9 years), 308 participants (11.0%) developed dementia, and 793 (28.4%) deceased. Individuals who were diagnosed with dementia were older (median age 75.2 vs 74.1 years) and were more often male (62.3% vs 54.2%). Mean baseline SBP, BMI, and non-HDL cholesterol did not differ significantly between both groups (Table 1).

The individual relationships for SBP, BMI, and non-HDL cholesterol with incident dementia are presented in Figure 2. For all these variables, the lowest quintile was associated with the highest adjusted HR for dementia compared with all other quintiles. Compared with the reference group (no risk factors with low values), fully adjusted HRs on dementia for individuals with 1, 2, and 3 low values were 1.18 (95% CI 0.93–1.51), 1.28 (95% CI 0.85–1.93), and 4.02 (95% CI 2.04–7.93), respectively (Table 2). Significant 2-way interactions were observed between low BMI and low non-HDL cholesterol levels (Table 3), suggesting that individuals with low BMI and low non-HDL had a 125% increased risk compared with those with higher values for these 2 factors (HR 2.25, 95% CI 1.41–3.60, p-interaction 0.01), which was substantially greater than for those with exclusively low BMI (HR 1.13, 95% CI 0.83–1.54) or low non-HDL (HR 0.89, 95% CI 0.61–1.30). Other 2-way interactions were not significant (p-interaction > 0.5).

In subgroup analyses, significant interactions with the number of low values for risk factors were observed for individuals with the ApoE4 genotype, a history of CVD, and those who used CLD at baseline (eTable 1, links.lww.com/WNL/C216). After Bonferroni correction for the number of subgroup analyses (n = 5, corrected $p < 0.01$), only the interaction with a history of CVD was significant (p-interaction = 0.009), suggesting that individuals with a history of CVD had a particularly higher risk (3 low values: HR 19.8, 95% CI 7.61–51.6) compared with those without (3 low values: HR 1.76, 95% CI 0.56–5.55).

The results for associations between the number of low values for SBP, BMI, and non-HDL cholesterol and dementia risk remained largely unchanged in sensitivity analyses using clinical cutoff points to define low values (eTable 2, links.lww.com/WNL/C216). No

Figure 1 Flowchart



BMI = body mass index; HDL = high-density lipoprotein; POE = preDIVA observational extension; preDIVA = Prevention of Dementia by Intensive Vascular Care; SBP = systolic blood pressure.

Table 1 Baseline Characteristics for Full Cohort and Individuals With and Without Dementia Diagnosis

	Overall (n = 2,789)	No dementia (n = 2,481)	Dementia (n = 308)	*p* Value
Age, y, median (IQR)	74.3 (72.1–76.3)	74.1 (72.0–76.2)	75.2 (72.7–77.1)	<0.001
Male sex, n (%)	1,536 (55.1)	1,344 (54.2)	192 (62.3)	0.008
Systolic blood pressure, mm Hg, mean (SD)	155.4 (21.3)	155.6 (21.2)	153.7 (21.9)	0.13
Diastolic blood pressure, mm Hg, mean (SD)	81.5 (10.9)	81.6 (10.9)	80.6 (10.9)	0.12
Antihypertensive medication use, n (%)	1,538 (55.2)	1,366 (55.1)	172 (56.0)	0.81
History of stroke, n (%)	289 (10.4)	250 (10.1)	39 (12.7)	0.19
History of cardiovascular disease, n (%)	823 (29.5)	743 (29.9)	80 (26.0)	0.17
History of diabetes mellitus type II, n (%)	497 (17.8)	435 (17.5)	62 (20.1)	0.30
Smoking status, n (%)				0.05
Current smoker	363 (13.0)	335 (13.5)	28 (9.1)	
Never	935 (33.5)	819 (33.0)	116 (37.7)	
Quit	1,491 (53.5)	1,327 (53.5)	164 (53.2)	
Body mass index, kg/m^2, mean (SD)	27.5 (4.20)	27.5 (4.2)	27.3 (4.4)	0.46
High-density lipoprotein, mmol/L, mean (SD)	1.5 (0.4)	1.5 (0.4)	1.6 (0.4)	0.02
Non–high-density lipoprotein, mmol/L, mean (SD)	3.7 (1.0)	3.7 (1.0)	3.8 (1.1)	0.79
Cholesterol-lowering drug use, n (%)	958 (34.4)	846 (34.2)	112 (36.5)	0.46
Total MMSE score median (IQR)	28 (27–29)	29 (27–29)	28 (26–29)	<0.001
Education				0.09
<7 y	666 (23.9)	577 (23.3)	89 (28.9)	
7–12 y	1,572 (56.4)	1,411 (56.9)	161 (52.3)	
>12 y	551 (19.8)	493 (19.9)	58 (18.8)	
ApoE4 positive, n (%)	772 (27.7)	615 (24.8)	157 (51.0)	<0.001

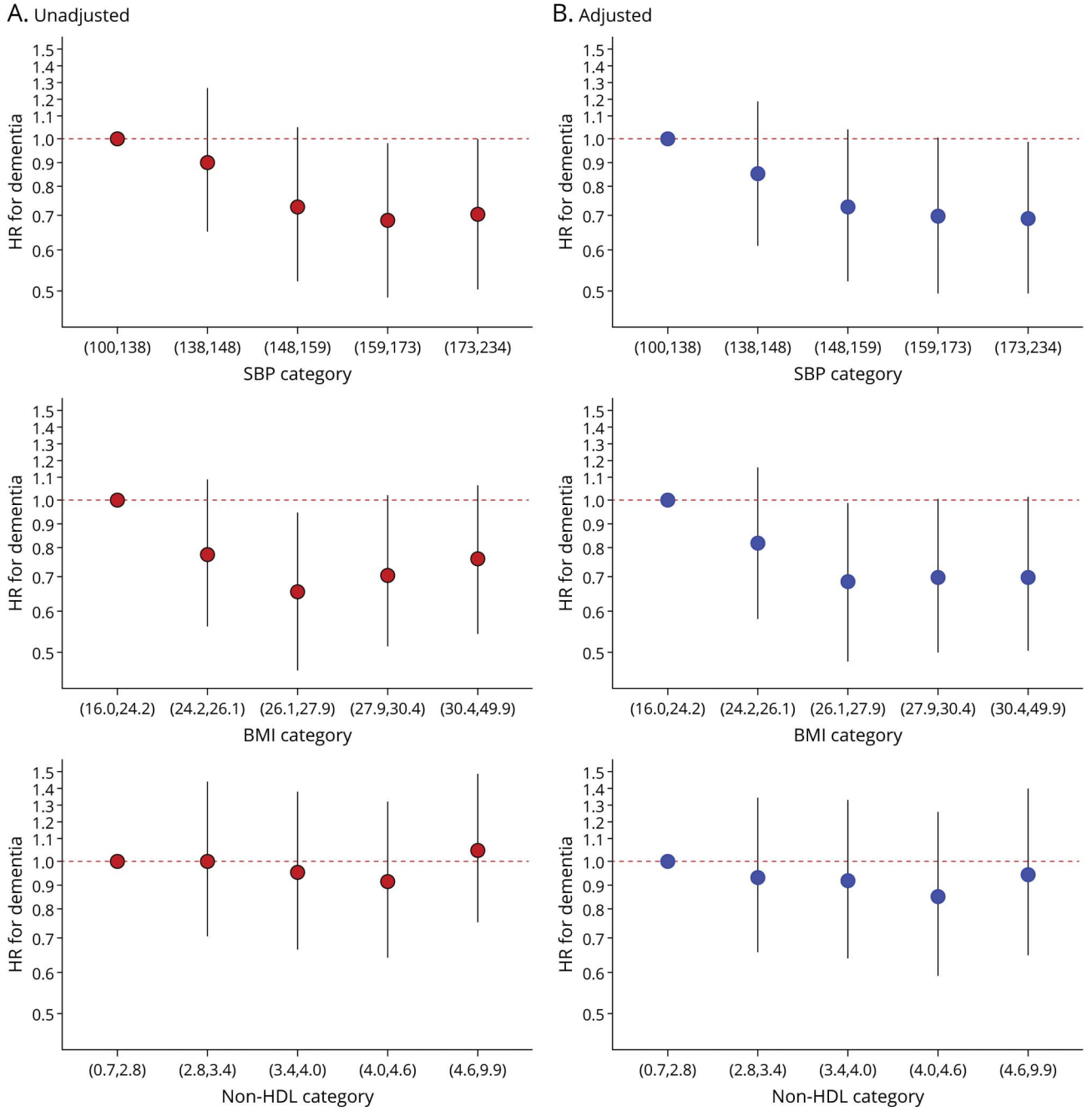
Abbreviations: IQR = interquartile range; MMSE = Mini-Mental State Examination.

specific combination of 2 individual risk factors with low values could explain the high risk observed in the group with 3 low values, and individuals with low values for all risk factors combined had a disproportionally higher HR for dementia compared with individuals in groups with 1 or 2 risk factors with low values (HR 3.19, 95% CI 1.63–6.26, eTable 3). In analyses according to median time to dementia diagnosis, similar results were observed with somewhat stronger effects in the group of individuals with a follow-up time below the median (<6.75 years 3 vs no low values: HR 4.55, 95% CI 1.96–10.56) compared with a longer (>6.75 years) follow-up time (3 vs no low values: HR 3.00, 95% CI 0.94–9.65, eTable 4). No differential effects were observed between randomization groups (eTable 5). Analyses with mortality as outcome showed increased HRs for individuals with 1, 2, and 3 low values compared with the reference group (no risk factors with a low value) (HR 1.07, 95% CI 0.92–1.25; HR 1.10, 95% CI 0.86–1.40; HR 1.37, 95% CI 0.79–2.39, respectively; *p* for trend 0.19, eTable 6). When dementia incidence and mortality were combined as outcome, HRs for participants with 1, 2, or 3 low values were HR 1.11, 95% CI 0.97–1.27; HR 1.13, 95% CI 0.92–1.41; and HR 1.48, 95% CI 0.90–2.44, respectively; *p* for trend 0.04 (eTable 7). Results of sensitivity analyses using data divided in tertiles were highly similar, although point estimates in those with 3 low risk factors strongly attenuated compared with the original analysis, suggesting that our results were particularly driven by more extreme low values (eTable 8). Sensitivity analyses using different measures for cholesterol and blood pressure yielded similar findings, although the associations for low diastolic blood pressure and high HDL cholesterol were less strong than those for systolic blood pressure and non-HDL cholesterol, respectively (eTables 9–12).

Discussion

This study including longitudinal data from community-dwelling older individuals aged 70–78 years at baseline showed that low values of SBP, BMI, and non-HDL cholesterol were associated with an increased risk of incident dementia over a

Figure 2 Association for Quintiles of Cardiovascular Risk Factors With Dementia Incidence



These figures display the relative association compared with the lowest quintile (reference) with dementia incidence for systolic blood pressure, BMI, and non-HDL cholesterol. (A) Unadjusted. (B) Adjusted for age at baseline, sex, education, history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and *APOE 4* genotype. BMI = body mass index; HDL = high-density lipoprotein; HR = hazard ratio; SBP = systolic blood pressure.

median follow-up of 10.3 years. Dementia risk was substantially higher in individuals with low values for all 3 risk factors than expected based on a dose-response relationship (302% vs 18% and 28% for 1 or 2 low values, respectively, compared with individuals without any low values). We did not observe any specific combination of 2 risk factors that could explain these results. The only observed interaction was between low BMI and low non-HDL cholesterol, which was associated with a 125% increase in dementia risk and therefore could not fully explain the 302% higher risk for individuals with low values for all 3 cardiovascular risk factors. Furthermore, low SBP was not associated with higher dementia risks in combination with low values for BMI or non-HDL cholesterol, but it strongly increased dementia risk in combination with low values for both risk factors. These results increase the plausibility that an overarching phenomenon, signaled by low values for multiple risk factors, may precede a clinical diagnosis of dementia. Competing risk of mortality could not explain our results.

Table 2 Associations Between the Number of Low Values of Systolic Blood Pressure, Body Mass Index, and Non-HDL Cholesterol, Based on Lowest Quintile, and Incident Dementia

No. of risk factors with low value	N total/dementia	Model 1 (N = 2,789) HR (95% CI)	Model 2 (N = 2,789) HR (95% CI)	Model 3 (N = 2,789) HR (95% CI)
No low	1,511/155	1	1	1
1 low	992/116	1.19 (0.94–1.52)	1.19 (0.94 1.52)	1.18 (0.93–1.51)
2 low	249/28	1.26 (0.84–1.88)	1.27 (0.85–1.91)	1.28 (0.85–1.93)
3 low	37/9	3.19 (1.63–6.26)	3.33 (1.69–6.53)	4.02 (2.04–7.93)
***p* for trend**		0.008	0.006	0.005

Abbreviations: HDL = high-density lipoprotein; HR = hazard ratio.
Cutoffs were systolic blood pressure ≤138 mm Hg, body mass index ≤24.2 kg/m^2, and non-HDL cholesterol ≤2.8 mmol/L. Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale.

These findings are in line with prior observational studies reporting contrasting associations for late-life SBP, BMI, and non-HDL cholesterol when assessed individually.[4,5,7,9,25,26] A pooled analysis of 2 population-based studies reported an inverse association between SBP and dementia risk, but only in AHM users.[26] A 2015 review on BMI and Alzheimer disease and dementia risk reported inverse associations in multiple studies.[7] Also, prior studies reported U-shaped associations for non-HDL cholesterol[6] and inverse associations for TC.[4,5] For LDL cholesterol, U-shaped associations were described in the general population on outcome mortality, not on incident dementia.[27] We used non-HDL cholesterol in

Table 3 Interactions Between Low Values of SBP, BMI, and Non-HDL Cholesterol, Based on Lowest Quintile, on Incident Dementia

Interaction	Model 1 (N = 2,789) HR (95% CI)	Model 2 (N = 2,789) HR (95% CI)	Model 3 (N = 2,789) HR (95% CI)
No low SBP or BMI	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI <24.2 (no low SBP)	1.38 (1.01–1.87)	1.36 (0.999–1.84)	1.32 (0.97–1.80)
SBP <138 (no low BMI)	1.35 (0.99–1.84)	1.34 (0.98–1.83)	1.33 (0.98–1.82)
Low SBP and low BMI	1.58 (0.99–2.50)	1.59 (1.00–2.53)	1.70 (1.07–2.71)
***p* for interaction**	0.6	0.7	0.9
No low SBP or non-HDL	1.00 (ref)	1.00 (ref)	1.00 (ref)
SBP <138 (no low non-HDL)	1.26 (0.94–1.70)	1.26 (0.94–1.70)	1.29 (0.95–1.73)
Non-HDL <2.8 (no low SBP)	1.00 (0.71–1.41)	1.03 (0.73–1.45)	1.07 (0.75–1.54)
Low SBP and low non-HDL cholesterol	1.60 (0.95–2.71)	1.65 (0.97–2.79)	1.73 (1.01–2.97)
***p* for interaction**	0.5	0.5	0.5
No low BMI or non-HDL	1.00 (ref)	1.00 (ref)	1.00 (ref)
BMI <24.2 (no low non-HDL)	1.15 (0.85–1.56)	1.14 (0.84–1.54)	1.13 (0.83–1.53)
Non-HDL <2.8 (no low BMI)	0.86 (0.60–1.23)	0.88 (0.61–1.26)	0.89 (0.61–1.30)
Low BMI and low non-HDL cholesterol	2.10 (1.32–3.32)	2.16 (1.36–3.43)	2.25 (1.41–3.60)
***p* for interaction**	0.02	0.02	0.01

Abbreviations: BMI = body mass index; HDL = high-density lipoprotein; HR = hazard ratio; SBP = systolic blood pressure.
A significant interaction between variables indicates that the effect of 1 variable depends on the level of the other variable in the interaction. Interpretation example: model 3, low BMI × non-HDL cholesterol: individuals with low BMI, without low non-HDL, had a 13% higher (HR = 1.13) dementia risk. Individuals with low non-HDL, without low BMI, had an 11% lower (HR = 0.89) dementia risk. The HR for low values for both variables was 2.25, indicating that individuals with low values for both variables have a 125% higher risk of dementia compared with individuals without low values for both variables. Model 1: adjusted for age at baseline; model 2: model 1 + sex, and education; model 3: model 2 + history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. All models used age as timescale.

our analyses because of its strong associations with cardiovascular events.[28-30] While previous studies focused on individual risk factors, the present study shows that these inverse relationships with dementia risk occur for multiple risk factors simultaneously, suggesting that particularly individuals with concurrent low values for the 3 risk factors studied here are at increased dementia risk, more than individuals with single, isolated low risk factor values.

Subgroup analyses suggested that the association between the number of risk factors with low values and dementia may be particularly strong in individuals with a history of CVD. This may be due to low values in this group signaling increased dementia risk in relatively vulnerable individuals. Also, in this group, low risk factor values may be more out of the ordinary. History of CVD is generally associated with relatively high values of cardiovascular risk factors, and therefore, low values in patients with CVD may be a more distinctive feature, and more often related to disease, than in those without CVD in whom low risk factor values are more common. Finally, if the low risk factor values are markers of an underlying state of (cardiovascular) aging beyond calendar years, such a state is likely to be present more often in individuals with a CVD history, which could also explain why low risk factor values more often indicate increased dementia risk.

A strength of this study is the integrated approach assessing the concurrent associations for multiple risk factor values and their interactions, whereas previous studies have mainly focused on studying individual risk factors independently. Thereby, this study can give an indication of the potential validity of the hypothesis that an overarching phenomenon, involving multiple risk factors, is associated with incipient disease, rather than individual risk factors. Other strengths of this study are the long follow-up duration (>10 years) and the complete follow-up for all-cause dementia (99.0%) and mortality (99.9%). Dementia diagnosis was established by an independent panel, and all diagnoses in preDIVA were reevaluated after 1 year to reduce the risk of a false-positive diagnosis.[18]

Our study has several limitations. First, our results may have been affected by selection bias because those who survived up to the age of inclusion and participated in the study are relatively healthy older individuals with less cardiovascular morbidity and mortality and better cognitive functioning. Selection of relatively healthy older individuals, or individuals who are less susceptible for the negative effects of high values for cardiovascular risk factors, could have contributed to an inverse relation with dementia incidence. However, the stronger associations in the CVD subgroup seemingly speak against this. Individuals with a history of CVD are likely relatively vulnerable to risk factor exposure, having developed disease previously. Therefore, the effects should be stronger in the non-CVD group if such survival bias would play a major role in our findings. Moreover, previous analyses have shown that participants of the preDIVA study are largely comparable, in terms of demographics and cardiovascular risk factors, with the overall Dutch population and with a large Dutch cohort study.[31] Second, the effect of medical treatment on the associations between low values for cardiovascular risk factors and dementia incidence is unknown. To address this issue, we performed subgroup analyses for baseline AHM and CLD use and observed no relevant or significant interactions, suggesting that this low risk factor phenomenon is independent of medication use and that it occurs both in patients with and without a chronic history of hypertension and/or dyslipidemia. Third, low values may in fact indicate declines of these risk factors over the preceding period, which have previously been associated with increased dementia risk. In our study, we were unable to assess the association between dementia risk and changes in risk factors over time because the data collected after baseline may have been affected by the preDIVA intervention. Fourth, the number of individuals and dementia cases with low values for all 3 risk factors was small, resulting in wide confidence intervals. In a post hoc sensitivity analysis defining low blood pressure, low BMI, and low non-HDL cholesterol based on the lowest tertile rather than lowest quintile, our results remained largely unchanged, although HRs for dementia in the group with 3 low risk factors strongly attenuated compared with the original analysis (HR 2.45 vs 4.02). Furthermore, we had insufficient data and power to analyze specific subtypes of all-cause dementia.

We showed that particularly individuals with a combination of low values for SBP, BMI, and non-HDL cholesterol are at an increased risk of dementia. Previous studies assessed the associations between individual risk factors and dementia risk. A case-control study of 962 participants reported weight loss in the years preceding dementia diagnosis, which the authors attributed to predementia apathy, loss of initiative, and reduced olfactory function.[32] The steep increase in risk for individuals with low values for all 3 cardiovascular risk factors combined in our study indicates that an overarching phenomenon, involving multiple risk factors, might precede a clinical dementia diagnosis, rather than risk factor-specific phenomena. This phenomenon might be either a multisystem state of decline that contributes to dementia (causal relation), an early sign of neurodegeneration as part of the disease (reverse causality), or a marker of physical aging beyond calendar age, which has been associated with increased dementia risk.[33] Our results are derived from observational data, and therefore, no statements about causality of the observed association can be made. Dementia has a long prodromal period, and studies have shown that cardiovascular risk factor values start to decline long before clinical symptoms of dementia occur.[15-17] However, in analyses according to time before dementia diagnosis, we observed stronger effects in short-term compared with long-term dementia cases. This finding is in line with a previous longitudinal cohort study, where no association with SBP measured 13 years before diagnosis was observed, but analyses with SBP measured 4 years before diagnosis showed an inverse association.[25] This might suggest that low values for risk factors are a marker of imminent dementia, rather than a cause.

In analyses with mortality as outcome, a combination of low values for SBP, BMI, and non-HDL cholesterol was associated with an increased risk of mortality. This suggests that the

relationship between low values and dementia risk is not affected by competing risk of death.

In midlife, high values for cardiovascular risk factors are widely acknowledged to increase dementia risk. However, this study shows that, in late life, low values of 3 important cardiovascular risk factors are associated with increased dementia risk in community-dwelling individuals. The risk of dementia was substantially higher for individuals with concomitant low values for SBP, BMI, and non-HDL cholesterol than for the sum of these individual associations, increasing the plausibility that an overarching phenomenon, involving multiple risk factors, is associated with increased dementia risk. If these results could be corroborated in other cohorts, we might be able to better identify older individuals at an increased risk for cognitive decline and dementia. It may also invite new risk prediction models for dementia specifically for older people, and this may contribute to future guidelines with respect to risk factor targets in older persons. Future studies will need to address the causality of this association or whether observations reflect merely prodromal signs of incipient dementia.

Acknowledgment

The authors thank all participants of the preDIVA trial and POE study and the members of the preDIVA trial and POE study teams for their help in data collection and management.

Study Funding

The preDIVA Trial was supported by the Dutch Ministry of Health, Welfare and Sports (grant number 50-50110-98-020), the Dutch Innovation Fund of Collaborative Health Insurances (grant number 05-234), and Netherlands Organization for Health Research and Development (grant number 62000015). E. Richard is funded by a personal grant from The Netherlands Organization for Health Research and Development (grant number 91718303). The preDIVA observational extension was supported by Alzheimer Nederland, project number wE.09-2017-08.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* December 6, 2021. Accepted in final form May 24, 2022. Submitted and externally peer reviewed. The handling editor was Linda Hershey, MD, PhD, FAAN.

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