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

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ABSTRACT

**Background and objectives:** Low values of blood pressure, Body Mass Index (BMI) and non-high density lipoproteine (non-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 are associated with 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 (IQR 7.0-10.9), 308 of 2789 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 one, two, and three 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 to those without any low values. This effect was not driven by any specific combination of two 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 to individuals without any low values. Dementia risk was substantially higher in individuals with low values for all three 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.

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INTRODUCTION

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).\textsuperscript{1, 2} However, in late life, low values for these risk factors have also been associated with increased dementia risk.\textsuperscript{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.\textsuperscript{9, 10} U-shaped associations with dementia have been described for non-High Density Lipoprotein (non-HDL) cholesterol levels\textsuperscript{6}, and inverse relations for late-life total cholesterol (TC) levels\textsuperscript{4, 5} and BMI.\textsuperscript{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.\textsuperscript{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 pathophysiological mechanisms have been proposed.\textsuperscript{6, 12, 13} However, as these relationships develop similarly with ageing 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. Firstly, 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.\textsuperscript{4} Second, contrasting associations in late life might reflect a state of impaired homeostasis across a range of physiological processes and organ systems, possibly contributing to the development of dementia or indicating increased dementia risk by being a marker of physical ageing beyond calendar years. Alternatively, the relationship may be retro-causal, 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 one time-point, it may therefore appear that individuals with low levels have the highest risk.\textsuperscript{11, 14-17} Lastly, 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.\textsuperscript{11}
Better identification of older individuals at 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 preDIVA trial and the preDIVA observational extension (POE) study.\textsuperscript{18,19} The preDIVA cluster-randomized trial compared the effect of intensive vascular care, i.e. 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 3526 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 endpoint or had not deceased during the preDIVA trial, resulting in information about dementia status in a total of 3491 participants (99%). Study protocols and outcomes have been published in detail elsewhere.\textsuperscript{18-20} Since there was no effect of the intervention, we considered the population as one cohort for the current study. This study is presented following the STROBE guidelines for observational cohort studies.\textsuperscript{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 two 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 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. 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 WHO criteria.\textsuperscript{18}

**DEMENTIA DIAGNOSIS**

The adjudication process for the outcome dementia has previously been described in detail.\textsuperscript{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 (DSM-IV).\textsuperscript{22} Participants underwent regular assessments every two years and at the final assessment, during the 6-8 years trial phase of preDIVA. Individuals with cognitive complaints, an MMSE score of $\leq 24$, a decline of $\geq 3$ points from baseline MMSE or $\geq 2$ points since the preceding two-yearly visit were referred to their general practitioner for clinical evaluation and adjudication by the outcome committee. All diagnoses were re-evaluated after one year. In case of drop-out, dementia status was retrieved from the general practitioner 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.\textsuperscript{23} Participants with a TICS score $>30$ and no formal dementia diagnosis were classified as not having dementia. In all other cases, the general practitioners’ 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 standard deviation when normally distributed. Not 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, since 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 versus any higher values based on quintiles (lowest quintile vs. all other quintiles). According to this dichotomization, each individual was assigned to one of four groups: 1) no low values, 2) one low value, 3) two low values, and 4) three 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 overall hazard ratio (HR) was calculated by including the number of low values as 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 three 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, as the associations might differ when risk factor values are low due to 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 cut-off values instead of quintiles (i.e. SBP 140 mmHg, BMI 25 kg/m2, 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.\textsuperscript{14, 15} Fourth, analyses according to randomization group were performed to investigate if there were differential effects between the intervention and control group of the original preDIVA trial, even though 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.\textsuperscript{24} Sixth, we repeated the main analysis with data divided in tertiles rather than quintiles, increasing the number of cases in each group. Lastly, 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 total cholesterol, 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).

\textbf{DATA AVAILABILITY}

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

\textbf{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.

\textbf{RESULTS}

A total of 2789 individuals with a median age of 74 years (IQR 72-76) were included in this analysis (Figure 1). Over a median follow-up of 10.3 years (IQR 7.0-10.9), 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 to all other quintiles. As compared to the reference group (no risk factors with low value), fully adjusted HRs on dementia for individuals with one, two, and three 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 two-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 to those with higher values for these two 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 two-way interactions were not significant (p-interaction>0.5).

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

The results for associations between number of low values for SBP, BMI and non-HDL cholesterol and dementia risk remained largely unchanged in sensitivity analyses using clinical cut-off points to define low values (eTable 2). No specific combination of two individual risk factors with low values could explain the high risk observed in the group with three low values, and individuals with low values for all risk factors combined had a disproportionally higher HR for dementia compared to individuals in groups with one or two 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 three vs. no low values: HR 4.55, 95%CI 1.96-10.56) compared to a longer (>6.75 years) follow-up time (three 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 one, two and three low values as compared to the reference group (no risk factors with 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 one, two or three low values were HR 1.11, 95%CI 0.97-1.27; HR 1.13, 95%CI 0.92-1.41; 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 three low risk factors strongly attenuated compared to 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 median follow-up of 10.3 years. Dementia risk was
substantially higher in individuals with low values for all three risk factors than expected based on a
dose-response relationship (302% versus 18% and 28% for one or two low values respectively,
compared to individuals without any low values). We did not observe any specific combination of two
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 three 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, signalled by low values for multiple risk factors, may precede a clinical diagnosis of
dementia. Competing risk of mortality could not explain our results.

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 two 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’s Disease and dementia risk reported
inverse associations in multiple studies.7 Also, prior studies reported U-shaped associations for non-
HDL cholesterol6 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 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 three 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 CVD patients 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) ageing 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.

STRENGTHS AND LIMITATIONS

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 is able to 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 re-evaluated after one year to reduce the risk of a false positive diagnosis.18

Our study has several limitations. First, our results may have been impacted by selection bias, since 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 that 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, since 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 three 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 three low risk factors strongly attenuated compared to the original analysis (HR 2.45 vs. HR 4.02). Furthermore, we had insufficient data and power to analyze specific subtypes of all-cause dementia.

INTERPRETATION AND MECHANISM

We showed that particularly individuals with a combination of low values for SBP, BMI and non-HDL cholesterol are at 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 pre-dementia
apathy, loss of initiative, and reduced olfactory function.\textsuperscript{32} The steep increase in risk for individuals with low values for all three 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 either be 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 ageing beyond calendar age, which has been associated with increased dementia risk.\textsuperscript{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.\textsuperscript{15-17} However, in analyses according to time before dementia diagnosis we observed stronger effects in short-term compared to 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.\textsuperscript{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.

**Clinical Relevance**

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 three 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 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.

TABLES AND FIGURES

Table 1. Baseline characteristics for full cohort and individuals with and without dementia diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 2789)</th>
<th>No dementia (n = 2481)</th>
<th>Dementia (n=308)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median [IQR]</td>
<td>74.3 [72.1, 76.3]</td>
<td>74.1 [72.0, 76.2]</td>
<td>75.2 [72.7, 77.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>1536 (55.1)</td>
<td>1344 (54.2)</td>
<td>192 (62.3)</td>
<td>0.008</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg, mean (SD)</td>
<td>155.4 (21.3)</td>
<td>155.6 (21.2)</td>
<td>153.7 (21.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg, mean (SD)</td>
<td>81.5 (10.9)</td>
<td>81.6 (10.9)</td>
<td>80.6 (10.9)</td>
<td>0.12</td>
</tr>
<tr>
<td>Antihypertensive medication use, n (%)</td>
<td>1538 (55.2)</td>
<td>1366 (55.1)</td>
<td>172 (56.0)</td>
<td>0.81</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>289 (10.4)</td>
<td>250 (10.1)</td>
<td>39 (12.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>History of cardiovascular disease, n (%)</td>
<td>823 (29.5)</td>
<td>743 (29.9)</td>
<td>80 (26.0)</td>
<td>0.17</td>
</tr>
<tr>
<td>History of diabetes mellitus type II, n (%)</td>
<td>497 (17.8)</td>
<td>435 (17.5)</td>
<td>62 (20.1)</td>
<td>0.30</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Current smoker</td>
<td>363 (13.0)</td>
<td>335 (13.5)</td>
<td>28 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>935 (33.5)</td>
<td>819 (33.0)</td>
<td>116 (37.7)</td>
<td></td>
</tr>
<tr>
<td>Quit</td>
<td>1491 (53.5)</td>
<td>1327 (53.5)</td>
<td>164 (53.2)</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index, kg/m², mean (SD)</td>
<td>27.5 (4.20)</td>
<td>27.5 (4.2)</td>
<td>27.3 (4.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>High density lipoprotein, mmol/L, mean (SD)</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.4)</td>
<td>1.6 (0.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-high density lipoprotein, mmol/L, mean (SD)</td>
<td>3.7 (1.0)</td>
<td>3.7 (1.0)</td>
<td>3.8 (1.1)</td>
<td>0.79</td>
</tr>
<tr>
<td>Cholesterol lowering drug use, n (%)</td>
<td>958 (34.4)</td>
<td>846 (34.2)</td>
<td>112 (36.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>Total MMSE score median [IQR]</td>
<td>28 [27, 29]</td>
<td>29 [27, 29]</td>
<td>28 [26, 29]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>&lt; 7 years</td>
<td>666 (23.9)</td>
<td>577 (23.3)</td>
<td>89 (28.9)</td>
<td></td>
</tr>
<tr>
<td>7-12 years</td>
<td>1572 (56.4)</td>
<td>1411 (56.9)</td>
<td>161 (52.3)</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>551 (19.8)</td>
<td>493 (19.9)</td>
<td>58 (18.8)</td>
<td></td>
</tr>
<tr>
<td>ApoE4 positive, n (%)</td>
<td>772 (27.7)</td>
<td>615 (24.8)</td>
<td>157 (51.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

APOE = Apolipoprotein E; IQR = interquartile range; MMSE = Mini Mental-State Examination; SD = Standard Deviation.
## Table 2. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia.

<table>
<thead>
<tr>
<th>Number of risk factors with low value</th>
<th>N total/dementia</th>
<th>Model 1 N=2789</th>
<th>Model 2 N=2789</th>
<th>Model 3 N=2789</th>
</tr>
</thead>
<tbody>
<tr>
<td>No low</td>
<td>1511/155</td>
<td>1 (95%CI)</td>
<td>1 (95%CI)</td>
<td>1 (95%CI)</td>
</tr>
<tr>
<td>One low</td>
<td>992/116</td>
<td>1.19 (0.94 – 1.52)</td>
<td>1.19 (0.94 – 1.52)</td>
<td>1.18 (0.93 – 1.51)</td>
</tr>
<tr>
<td>Two low</td>
<td>249/28</td>
<td>1.26 (0.84 – 1.88)</td>
<td>1.27 (0.85 – 1.91)</td>
<td>1.28 (0.85 – 1.93)</td>
</tr>
<tr>
<td>Three low</td>
<td>37/9</td>
<td>3.19 (1.63 – 6.26)</td>
<td>3.33 (1.69 – 6.53)</td>
<td>4.02 (2.04 – 7.93)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.008</td>
<td>0.006</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

Cut-offs were: systolic blood pressure ≤138mmHg, Body Mass Index ≤24.2 kg/m², 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. HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

## Table 3. Interactions between low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol - based on lowest quintile - on incident dementia.

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Model 1 N=2789</th>
<th>Model 2 N=2789</th>
<th>Model 3 N=2789</th>
</tr>
</thead>
<tbody>
<tr>
<td>No low SBP or BMI</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>BMI &lt; 24.2 (no low SBP)</td>
<td>1.38*</td>
<td>1.36</td>
<td>1.32</td>
</tr>
<tr>
<td></td>
<td>(1.01 – 1.87)</td>
<td>(0.999 – 1.84)</td>
<td>(0.97 – 1.80)</td>
</tr>
<tr>
<td>SBP &lt; 138 (no low BMI)</td>
<td>1.35</td>
<td>1.34</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td>(0.99 – 1.84)</td>
<td>(0.98 – 1.83)</td>
<td>(0.98 – 1.82)</td>
</tr>
<tr>
<td>Low SBP and low BMI</td>
<td>1.58</td>
<td>1.59</td>
<td>1.70</td>
</tr>
<tr>
<td></td>
<td>(0.99 – 2.50)</td>
<td>(1.00 – 2.53)</td>
<td>(1.07 – 2.71)</td>
</tr>
<tr>
<td>P for interaction</td>
<td>0.6</td>
<td>0.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

| No low SBP or non-HDL                    | 1.00 (ref)     | 1.00 (ref)     | 1.00 (ref)     |
| SBP < 138 (no low non-HDL)               | 1.26           | 1.26           | 1.29           |
|                                          | (0.94 – 1.70)  | (0.94 – 1.70)  | (0.95 – 1.73)  |
| non-HDL < 2.8 (no low SBP)               | 1.00           | 1.03           | 1.07           |
|                                          | (0.71 – 1.41)  | (0.73 – 1.45)  | (0.75 – 1.54)  |
| Low SBP and low non-HDL cholesterol      | 1.60           | 1.65           | 1.73           |
|                                          | (0.95 – 2.71)  | (0.97 – 2.79)  | (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           | 1.14           | 1.13           |
|                                          | (0.85 – 1.56)  | (0.84 – 1.54)  | (0.83 – 1.53)  |
A significant interaction between variables indicates that the effect of one 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 to 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. BMI = Body Mass Index; HDL = High-density lipoprotein; HR = hazard ratio; SBP = systolic blood pressure; 95%CI = 95% confidence interval.

Figure 1. Flowchart

POE = preDIVA Observational Extension; SBP = systolic blood pressure; BMI = Body Mass Index; non-HDL = non-High Density Lipoprotein
Figure 2. Association for quintiles of cardiovascular risk factors with dementia incidence.

These figures display the relative association compared to the lowest quintile (reference) with dementia incidence for systolic blood pressure, BMI, and non-HDL cholesterol. (B) Adjusted for age at baseline, sex, education, history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype.
REFERENCES

Low Values for Blood Pressure, BMI, and Non-HDL Cholesterol and the Risk of Late-Life Dementia
Melina GHE den Brok, Esmé Eggink, Marieke P Hoevenaar-Blom, et al.
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