

Supplemental Material

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Table of content

		Page
eTable 1	Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia in pre-defined subgroups.	2
eTable 2	Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, <u>based on clinical cut-off points</u> , and incident dementia.	3
eTable 3	Sensitivity analyses for specific combinations of low values for systolic blood pressure, Body Mass Index and non-HDL cholesterol based on lowest quintile and incident dementia risk.	4
eTable 4	Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, <u>according to median time to dementia diagnosis based on lowest quintile</u> , and incident dementia.	4
eTable 5	Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia in sensitivity analyses <u>according to randomization group</u> .	5
eTable 6	Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and <u>mortality</u> .	5
eTable 7	Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and <u>incident dementia and mortality combined</u> .	6
eTable 8	Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, <u>based on lowest tertile instead of lowest quintile</u> , and incident dementia.	6
eTable 9	Associations between number of low values of systolic blood pressure, Body Mass Index, and <u>total cholesterol instead of non-HDL cholesterol</u> , based on lowest quintile, and incident dementia.	7
eTable 10	Associations between number of low values of systolic blood pressure, Body Mass Index, and <u>LDL cholesterol instead of non-HDL cholesterol</u> , based on lowest quintile, and incident dementia.	7
eTable 11	Associations between number of low values of systolic blood pressure (lowest quintile), Body Mass Index (lowest quintile), and high values of <u>HDL cholesterol (highest quintile) instead of non-HDL cholesterol</u> and incident dementia.	8
eTable 12	Associations between number of low values of <u>diastolic blood pressure instead of systolic blood pressure</u> , Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia.	9

eTable 1. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia in pre-defined subgroups.

	N	Number of risk factors with low value, HR (95%CI)				P for interaction
		No low	One low	Two low	Three Low	
Sex						0.3
Female	1253	1.0	1.19 (0.79-1.80)	1.38 (0.73-2.61)	8.91 (3.64-21.83)	
Male	1536	1.0	1.16 (0.86-1.57)	1.26 (0.74-2.17)	1.82 (0.57-5.80)	
ApoE4 genotype						0.02
Positive	772	1.0	1.59 (1.14-2.22)	1.02 (0.54-1.96)	4.54 (1.38-14.96)	
Negative	2017	1.0	0.81 (0.56-1.18)	1.58 (0.93-2.69)	3.72 (1.60-8.62)	
History of CVD						0.009
Yes	823	1.0	1.35 (0.82-2.21)	1.60 (0.78-3.30)	19.81 (7.61-51.58)	
No	1966	1.0	1.16 (0.87-1.53)	1.26 (0.77-2.08)	1.76 (0.56-5.55)	
Antihypertensive medication use	1538					0.3
Yes	1247	1.0	1.22 (0.88-1.69)	1.11 (0.60-2.06)	5.95 (2.68-13.18)	
No		1.0	1.15 (0.79-1.69)	1.34 (0.75-2.40)	2.23 (0.51-9.72)	
Cholesterol lowering drug use						0.05 [#]
Yes	958	1.0	1.13 (0.74-1.71)	0.99 (0.49-1.97)	5.63 (2.69-11.78)	
No	1826	1.0	1.23 (0.91-1.67)	1.45 (0.87-2.44)	-*	

Cut-offs were: systolic blood pressure ≤ 138 mmHg, Body Mass Index ≤ 24.2 kg/m², nonHDL-cholesterol ≤ 2.8 mmol/L. Fully adjusted model (model 3): adjusted for sex, education, history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. Age was used as timescale. AHM = antihypertensive medication; ApoE = Apolipoprotein; CVD = cardiovascular disease; HDL = High-density lipoprotein; HR = hazard ratio; ref. = reference; 95%CI = 95% confidence interval. * Calculation of HR not possible because there were no dementia cases in the group of individuals that did not use cholesterol-lowering drugs. [#]P=0.049.

eTable 2. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on clinical cut-off points, and incident dementia.

		Model 1 N=2789	Model 2 N=2789	Model 3 N=2789
Number of risk factors with low value	N total/dementia	HR (95%CI)	HR (95%CI)	HR (95%CI)
No low	996/109	1	1	1
One low	1202/116	0.92 (0.71 – 1.20)	0.94 (0.72 – 1.22)	0.94 (0.72 – 1.22)
Two low	499/63	1.27 (0.93 – 1.73)	1.29 (0.94 – 1.76)	1.28 (0.93 – 1.75)
Three low	92/20	2.43 (1.51 – 3.92)	2.47 (1.53 – 3.98)	2.78 (1.72 – 4.50)
<i>P for trend</i>		<i>0.005</i>	<i>0.004</i>	<i>0.002</i>

Cut-offs were: systolic blood pressure ≤ 140 mmHg, Body Mass Index ≤ 25 kg/m², nonHDL-cholesterol ≤ 3.4 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.

eTable 3. Sensitivity analyses for specific combinations of low values for systolic blood pressure, Body Mass Index and non-HDL cholesterol based on lowest quintile and incident dementia risk.

	No dementia cases	Dementia cases	HR (95%CI)
no low	1356	155	1 (ref)
Low non-HDL cholesterol	285	29	0.91 (0.61 – 1.35)
Low BMI	296	42	1.27 (0.90 – 1.79)
Low SBP	295	45	1.39 (1.0 [#] – 1.94)
Low SBP & low non-HDL cholesterol	66	6	0.98 (0.43 – 2.22)
Low SBP & low BMI	100	11	1.09 (0.59 – 2.01)
Low non-HDL cholesterol & low BMI	55	11	1.80 (0.98 – 3.32)
Low SBP, low BMI & low non-HDL cholesterol	28	9	3.19 (1.63 – 6.26)

This analysis shows the association with dementia risk for low values for systolic blood pressure, Body Mass Index and non-HDL cholesterol individually, and in combination compared to no low values for any of these risk factors. Fully adjusted model (model 3): adjusted for sex, education, history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. Age was used as timescale. Abbreviations: SBP = systolic blood pressure; HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval. [#]Lower 95%CI=0.999.

eTable 4: Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, according to median time to dementia diagnosis based on lowest quintile, and incident dementia.

Number of risk factors with low value	time to dementia <6.75 years		time to dementia ≥6.75 years	
	N total/dementia	HR (95%CI)	N total/dementia	HR (95%CI)
No low	1511/72	1	1147/80	1
One low	992/60	1.31 (0.93 – 1.85)	785/55	1.00 (0.71 - 1.42)
Two low	249/16	1.48 (0.86 – 2.57)	194/16	1.35 (0.78 – 2.34)
Three low	37/6	4.55 (1.96 – 10.56)	26/3	3.00 (0.93 – 9.65)
<i>P for trend</i>		<i>0.005</i>		<i>0.2</i>

Cut-offs for lowest quintiles differed slightly in the respective groups (<median/>median): systolic blood pressure ≤138/138.5mmHg, Body Mass Index ≤24.2/24.2 kg/m², nonHDL-cholesterol ≤2.8/2.9 mmol/L. Fully adjusted model (model 3): adjusted for sex, education, history of stroke, cardiovascular disease or diabetes mellitus, smoking status, and APOE 4 genotype. Age was used as timescale. HDL = High-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

eTable 5. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia in sensitivity analyses according to randomization group.

	Study arm	
	Intervention	Control
Number of individuals	1510	1279
No low, HR (95%CI)	1.0	1.0
One low, HR (95%CI)	1.29 (0.93-1.79)	1.05 (0.72-1.52)
Two low, HR (95%CI)	1.55 (0.94-2.57)	0.97 (0.48-1.98)
Three low, HR (95%CI)	1.79 (0.44-7.35)	6.99 (3.07-15.92)
P for interaction	0.2	

Abbreviations: HR = hazard ratio; 95%CI = 95% confidence interval.

eTable 6. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and mortality.

		Model 1 N=2788	Model 2 N=2788	Model 3 N=2788
Number of risk factors with low value	N total/event (mortality)	HR (95%CI)	HR (95%CI)	HR (95%CI)
No low	1511/403	1	1	1
One low	991/297	1.16 (1.00 – 1.35)	1.17 (1.00 – 1.35)	1.07 (0.92 – 1.25)
Two low	249/80	1.35 (1.06 – 1.71)	1.32 (1.04 – 1.68)	1.10 (0.86 – 1.40)
Three low	37/13	1.67 (0.96 – 2.90)	1.61 (0.93 – 2.80)	1.37 (0.79 – 2.39)
<i>P for trend</i>		<i>0.002</i>	<i>0.003</i>	<i>0.2</i>

Cut-offs were: systolic blood pressure ≤ 138 mmHg, Body Mass Index ≤ 24.2 kg/m², nonHDL-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.

eTable 7. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia and mortality combined.

		Model 1 N=2789	Model 2 N=2789	Model 3 N=2789
Number of risk factors with low value	N total/event (dementia+mortality)	HR (95%CI)	HR (95%CI)	HR (95%CI)
No low	1511/528	1	1	1
One low	992/391	1.18 (1.03 – 1.34)	1.17 (1.03 – 1.34)	1.11 (0.97 – 1.27)
Two low	249/102	1.32 (1.07 – 1.63)	1.30 (1.06 – 1.61)	1.13 (0.92 – 1.41)
Three low	37/16	1.58 (0.96 – 2.60)	1.56 (0.95 – 2.57)	1.48 (0.90 – 2.44)
<i>P for trend</i>		<i>0.0006</i>	<i>0.0008</i>	<i>0.04</i>

Cut-offs were: systolic blood pressure ≤ 138 mmHg, Body Mass Index ≤ 24.2 kg/m², nonHDL-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.

eTable 8. Associations between number of low values of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest tertile instead of lowest quintile, and incident dementia.

		Model 1 N=2789	Model 2 N=2789	Model 3 N=2789
Number of risk factors with low value	N total/dementia	HR (95%CI)	HR (95%CI)	HR (95%CI)
No low	897/87	1	1	1
One low	1191/122	1.12 (0.85 – 1.47)	1.13 (0.86 - 1.49)	1.11 (0.84 – 1.46)
Two low	578/79	1.53 (1.13 – 2.08)	1.55 (1.14 – 2.10)	1.51 (1.11 – 2.05)
Three low	123/20	2.12 (1.30 – 3.45)	2.18 (1.34 – 3.55)	2.45 (1.50 – 4.01)
<i>P for trend</i>		<i><0.001</i>	<i><0.001</i>	<i><0.001</i>

Cut-offs were: systolic blood pressure ≤ 145 mmHg, Body Mass Index ≤ 25.5 kg/m², non-HDL cholesterol ≤ 3.2 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.

eTable 9. Associations between number of low values of systolic blood pressure, Body Mass Index, and total cholesterol instead of non-HDL cholesterol, based on lowest quintile, and incident dementia.

		Model 1 N=2789	Model 2 N=2789	Model 3 N=2789
Number of risk factors with low value	N total/dementia	HR (95%CI)	HR (95%CI)	HR (95%CI)
No low	1461/155	1	1	1
One low	1044/121	1.17 (0.92 – 1.48)	1.18 (0.93 - 1.50)	1.16 (0.92 – 1.48)
Two low	251/24	1.05 (0.69 – 1.62)	1.08 (0.70 – 1.66)	1.08 (0.70 – 1.68)
Three low	33/8	3.36 (1.65 – 6.84)	3.64 (1.78 – 7.46)	5.30 (2.57 – 10.95)
<i>P for trend</i>		<i>0.05</i>	<i>0.03</i>	<i>0.03</i>

Cut-offs were: systolic blood pressure ≤ 138 mmHg, Body Mass Index ≤ 24.2 kg/m², total cholesterol ≤ 4.3 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. HR = hazard ratio; 95%CI = 95% confidence interval.

eTable 10. Associations between number of low values of systolic blood pressure, Body Mass Index, and LDL cholesterol instead of non-HDL cholesterol, based on lowest quintile, and incident dementia.

		Model 1 N=2787	Model 2 N=2787	Model 3 N=2787
Number of risk factors with low value	N total/dementia	HR (95%CI)	HR (95%CI)	HR (95%CI)
No low	1449/149	1	1	1
One low	1044/118	1.16 (0.91 – 1.47)	1.16 (0.91 - 1.48)	1.14 (0.89 – 1.46)
Two low	260/31	1.33 (0.90 – 1.96)	1.35 (0.92 – 1.99)	1.34 (0.90 – 1.98)
Three low	34/9	3.52 (1.79 – 6.90)	3.69 (1.88 – 7.24)	4.67 (2.36 – 9.23)
<i>P for trend</i>		<i>0.005</i>	<i>0.004</i>	<i>0.005</i>

Cut-offs were: systolic blood pressure ≤ 138 mmHg, Body Mass Index ≤ 24.2 kg/m², LDL cholesterol ≤ 2.3 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. LDL = Low-density lipoprotein; HR = hazard ratio; 95%CI = 95% confidence interval.

eTable 11. Associations between number of low values of systolic blood pressure (lowest quintile), Body Mass Index (lowest quintile), and high values of HDL cholesterol (highest quintile) instead of non-HDL cholesterol and incident dementia.

		Model 1 N=2789	Model 2 N=2789	Model 3 N=2789
Number of risk factors with low value	N total/dementi a	HR (95%CI)	HR (95%CI)	HR (95%CI)
No low	1542/149	1	1	1
One low	923/113	1.27 (1.00 – 1.63)	1.25 (0.98 - 1.60)	1.26 (0.98 – 1.62)
Two low	269/36	1.40 (0.98 – 2.02)	1.39 (0.97 – 2.01)	1.50 (1.03 – 2.18)
Three low	55/10	2.41 (1.27 – 4.57)	2.38 (1.25 – 4.54)	2.35 (1.23 – 4.50)
<i>P for trend</i>		<i>0.002</i>	<i>0.003</i>	<i>0.002</i>

Cut-offs were: systolic blood pressure ≤ 138 mmHg, Body Mass Index ≤ 24.2 kg/m², HDL cholesterol ≥ 1.8 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.

eTable 12. Associations between number of low values of diastolic blood pressure instead of systolic blood pressure, Body Mass Index, and non-HDL cholesterol, based on lowest quintile, and incident dementia.

		Model 1 N=2787	Model 2 N=2787	Model 3 N=2787
Number of risk factors with low value	N total/dementi a	HR (95%CI)	HR (95%CI)	HR (95%CI)
No low	1480/151	1	1	1
One low	986/111	1.14 (0.89 – 1.46)	1.14 (0.89 1.46)	1.13 (0.88 – 1.45)
Two low	291/38	1.36 (0.95 – 1.94)	1.36 (0.95 – 1.94)	1.36 (0.94 – 1.96)
Three low	30/7	2.45 (1.15 – 5.23)	2.66 (1.24 – 5.70)	2.38 (1.10 – 5.15)
<i>P for trend</i>		<i>0.02</i>	<i>0.01</i>	<i>0.03</i>

Cut-offs were: diastolic blood pressure ≤ 72.5 mmHg, 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.