

Association of metabolic syndrome with incident dementia: role of number and age at measurement of components in a 28-year follow-up of the Whitehall II cohort study

Marcos D. Machado-Fragua

Aurore Fayosse

Manasa-Shanta Yerramalla

Thomas van Sloten

Adam Tabak

Mika Kivimaki

Séverine Sabia

Archana Singh-Manoux

Supplementary data

Table S1. Sample characteristics at <60, 60 to <70, and ≥ 70 years overall and according to dementia status at the end of follow-up (31st March 2019).

Table S2. Role of the number of metabolic components at <60, 60 to <70, and ≥ 70 years on the association between metabolic syndrome and incidence of dementia.

Table S3. Association between metabolic syndrome components at <60, 60 to <70, and ≥ 70 years and incidence of dementia using inverse probability weighting to account for missing data.

Table S4. Association between the number of MetS components at <60, 60 to <70, and ≥ 70 years and incidence of dementia using inverse probability weighting to account for missing data.

Table S5. Alternate cutoff points to define metabolic risk at <60, 60 to <70, and ≥ 70 years and incidence of dementia using inverse probability weighting to account for missing data.

Figure S1. Flow chart of sample selection.

Figure S2. Association of number of metabolic syndrome components at age <60 (A), 60 to <70 (B), and ≥ 70 years (C) with dementia using restricted cubic splines.

Figure S3. Multistate models for the role of “high metabolic risk” at age <60 years in transition to cardiovascular disease (stroke, coronary heart disease or heart failure) and dementia using inverse probability weighting to account for missing data.

Table S1. Sample characteristics at <60, 60 to <70, and ≥70 years overall and according to dementia status at the end of follow-up (31st March 2019).

	Total population	Dementia		P-value [§]
		No	Yes	
At age <60 years*				
Age, M(SD)	55.1 (2.9)	55.0 (2.9)	55.0 (2.9)	0.58
Sex, women	2219 (30.5)	2074 (30.2)	145 (36.9)	0.005
Education, low	3249 (44.7)	3029 (44.1)	220 (56.0)	<0.001
Ethnicity, non-white	719 (9.9)	656 (9.6)	63 (16.0)	<0.001
Smoking, current smokers	846 (11.6)	796 (11.6)	50 (12.7)	0.76
Alcohol consumption, moderate drinkers	3881 (53.4)	3704 (53.9)	177 (45.0)	<0.001
Fruits and vegetables consumption, ≥twice/day	2235 (30.8)	2157 (31.4)	78 (19.9)	<0.001
Physical activity (moderate - vigorous), h/week, M(SD)	3.3 (3.6)	3.3 (3.5)	3.3 (3.5)	0.15
Use of lipid-lowering drugs	280 (3.9)	270 (3.9)	10 (2.5)	0.17
Use of antihypertensive drugs	953 (13.1)	883 (12.9)	70 (17.8)	0.01
Use of glucose-lowering drugs,	118 (1.6)	106 (1.5)	12 (3.1)	0.02
Metabolic syndrome components				
Elevated WC	1286 (17.7)	1215 (17.7)	71 (18.1)	0.85
Elevated triglycerides	2163 (29.8)	2040 (29.7)	123 (31.3)	0.50
Low HDL-C	1311 (18.1)	1224 (17.8)	87 (22.1)	0.03
Elevated blood pressure	3193 (44.0)	2984 (43.4)	209 (53.2)	<0.001
Elevated fasting glucose	1662 (22.9)	1562 (22.7)	100 (25.5)	0.21
At age 60 to <70 years[†]				
Age, M(SD)	65.0 (1.5)	65.0 (1.5)	65.0 (1.5)	0.50
Sex, women	1949 (29.3)	1796 (28.8)	153 (36.7)	0.001
Education, low	2916 (43.8)	2679 (42.9)	237 (56.8)	<0.001
Ethnicity, non-white	559 (8.4)	501 (8.0)	58 (13.9)	<0.001
Smoking, current smokers	433 (6.5)	402 (6.4)	31 (7.4)	0.20
Alcohol consumption, moderate drinkers	3589 (53.9)	3387 (54.3)	202 (48.4)	<0.001
Fruits and vegetables consumption, ≥twice/day	2733 (41.0)	2592 (41.5)	141 (33.8)	<0.001
Physical activity (moderate - vigorous), h/week, M(SD)	4.0 (3.6)	4.0 (3.6)	4.0 (3.6)	0.74
Use of lipid-lowering drugs	1611 (24.2)	1541 (24.7)	70 (16.8)	<0.001
Use of antihypertensive drugs	2085 (31.3)	1956 (31.3)	129 (30.9)	0.87
Use of glucose-lowering drugs,	307 (4.6)	280 (4.5)	27 (6.5)	0.06
Metabolic syndrome components				
Elevated WC	1900 (28.5)	1801 (28.9)	99 (23.7)	0.03
Elevated triglycerides	2608 (39.2)	2460 (39.4)	148 (35.5)	0.11
Low HDL-C	2109 (31.7)	1987 (31.8)	122 (29.3)	0.28
Elevated blood pressure	3876 (58.2)	3631 (58.2)	245 (58.8)	0.81
Elevated fasting glucose	1715 (25.8)	1596 (25.6)	119 (28.5)	0.18
At age ≥70 years[‡]				
Age, M(SD)	73.9 (1.9)	73.9 (1.9)	73.9 (1.9)	0.09
Sex, women	1060 (29.4)	969 (29.0)	91 (34.5)	0.05
Education, low	1766 (49.0)	1611 (48.2)	155 (58.7)	0.002
Ethnicity, non-white	348 (9.7)	309 (9.2)	39 (14.8)	0.003
Smoking, current smokers	108 (3.0)	103 (3.1)	5 (1.9)	0.53
Alcohol moderate, moderate drinkers	1984 (55.0)	1855 (55.5)	129 (48.9)	<0.001
Fruits and vegetables consumption, ≥twice/day	1450 (40.2)	1370 (41.0)	80 (30.3)	0.002
Physical activity (moderate - vigorous), h/week, M(SD)	3.5 (3.3)	3.5 (3.3)	3.5 (3.3)	0.20
Use of lipid-lowering drugs	1667 (46.2)	1545 (46.2)	122 (46.2)	0.99
Use of antihypertensive drugs	1798 (49.8)	1651 (49.4)	147 (55.7)	0.04
Use of glucose-lowering drugs,	258 (7.2)	228 (6.8)	30 (11.4)	0.01
Metabolic syndrome components				
Elevated WC	1281 (35.5)	1194 (35.7)	87 (33.0)	0.37

Elevated triglycerides	1923 (53.3)	1781 (53.3)	142 (53.8)	0.87
Low HDL-C	1810 (50.2)	1679 (50.2)	131 (49.6)	0.85
Elevated blood pressure	2602 (72.1)	2407 (72.0)	195 (73.9)	0.51
Elevated fasting glucose	977 (27.1)	885 (26.5)	92 (34.9)	0.003

M: mean; SD: standard deviation; WC: waist circumference; HDL-C: high density lipoprotein-cholesterol; Data are n (%), unless otherwise specified

* Mean (SD) age at assessment=55.1 (2.9) years; † Mean (SD) age at assessment=65.0 (1.5) years; ‡ Mean (SD) age at assessment=73.9 (1.9) years

§ p-value for difference in χ^2 test (categorical data) or student's *t* test (continuous) data.

Table S2. Role of the number of metabolic components at <60, 60 to <70, and ≥70 years on the association between metabolic syndrome and incidence of dementia.

Number of MetS components	N Dementia cases/Total	Rate of dementia/1000 person-years	HR (95% CI)	
			Model 1 [§]	Model 2
At age <60 years*, Median (IQR) follow-up 20.8 (15.5, 26.2) years				
0	97/2325	2.08	1 (Ref.)	1 (Ref.)
1	123/2145	2.85	1.29 (0.99, 1.68)	1.25 (0.96, 1.63)
2	92/1493	3.21	1.57 (1.17, 2.09)	1.48 (1.11, 1.98)
MetS (3-5)	81/1302	3.34	1.58 (1.17, 2.13)	1.50 (1.11, 2.02)
At age 60 years to <70 years[†], Median (IQR) follow-up 10.4 (6.4, 15.6) years				
0	75/1409	4.65	1 (Ref.)	1 (Ref.)
1	127/1753	6.20	1.30 (0.98, 1.73)	1.28 (0.96, 1.71)
2	100/1387	6.31	1.42 (1.05, 1.92)	1.38 (1.02, 1.86)
MetS (3-5)	115/2111	5.65	1.49 (1.11, 2.01)	1.40 (1.04, 1.89)
At age ≥70 years[‡], Median (IQR) follow-up 4.2 (3.1, 7.1) years				
0	23/442	8.90	1 (Ref.)	1 (Ref.)
1	57/729	13.26	1.49 (0.92, 2.42)	1.44 (0.88, 2.34)
2	48/650	12.81	1.50 (0.91, 2.47)	1.45 (0.88, 2.39)
MetS (3-5)	136/1787	13.49	1.54 (0.99, 2.40)	1.47 (0.94, 2.30)

MetS: Metabolic syndrome

* Mean (SD) age at assessment=55.1 (2.9) years

[†] Mean (SD) age at assessment=65.0 (1.5) years

[‡] Mean (SD) age at assessment=73.9 (1.9) years

[§] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)

^{||} Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

Table S3. Association between metabolic syndrome components at <60, 60 to <70, and ≥70 years and incidence of dementia using inverse probability weighting to account for missing data.

	Elevated WC		Elevated triglycerides		Low HDL-C		Elevated blood pressure		Elevated fasting glucose	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
At age <60 years*, Median (IQR) follow-up 20.8 (15.5, 26.2) years										
Dementia cases/total, No	322/5979	71/1286	270/5102	123/2163	306/5954	87/1311	184/4072	209/3193	293/5603	100/1662
Rate/1000 person-years	2.78	3.21	2.79	2.98	2.69	3.58	2.40	3.42	2.74	3.22
Cox regression, HR (95% CI)										
Model 1 [§]	1 (Ref.)	1.42 (1.09, 1.84)	1 (Ref.)	1.06 (0.85, 1.32)	1 (Ref.)	1.32 (1.04, 1.67)	1 (Ref.)	1.33 (1.09, 1.62)	1 (Ref.)	1.19 (0.94, 1.50)
Model 2	1 (Ref.)	1.36 (1.05, 1.77)	1 (Ref.)	1.00 (0.81, 1.25)	1 (Ref.)	1.29 (1.01, 1.64)	1 (Ref.)	1.31 (1.07, 1.60)	1 (Ref.)	1.18 (0.94, 1.50)
At age 60 years to <70 years†, Median (IQR) follow-up 10.4 (6.4, 15.6) years										
Dementia cases/total, No	318/4760	99/1900	269/4052	148/2608	295/4551	122/2109	172/2784	245/3876	298/4945	119/1715
Rate/1000 person-years	5.88	5.54	5.83	5.71	5.65	6.14	5.71	5.84	5.52	6.58
Cox regression, HR (95% CI)										
Model 1 [§]	1 (Ref.)	1.06 (0.84, 1.36)	1 (Ref.)	1.17 (0.96, 1.44)	1 (Ref.)	1.31 (1.06, 1.63)	1 (Ref.)	1.00 (0.82, 1.22)	1 (Ref.)	1.35 (1.08, 1.70)
Model 2	1 (Ref.)	1.01 (0.79, 1.29)	1 (Ref.)	1.14 (0.92, 1.40)	1 (Ref.)	1.26 (1.01, 1.56)	1 (Ref.)	0.98 (0.80, 1.20)	1 (Ref.)	1.33 (1.05, 1.67)
At age ≥70 years‡, Median (IQR) follow-up 4.2 (3.1, 7.1) years										
Dementia cases/total, No	177/2327	87/1281	122/1685	142/1923	133/1798	131/1810	69/1006	195/2602	172/2631	92/977
Rate/1000 person-years	15.30	13.72	14.03	15.37	14.17	15.32	14.32	14.89	12.96	19.30
Cox regression, HR (95% CI)										
Model 1 [§]	1 (Ref.)	0.94 (0.71, 1.24)	1 (Ref.)	1.11 (0.86, 1.43)	1 (Ref.)	1.11 (0.86, 1.43)	1 (Ref.)	0.99 (0.74, 1.32)	1 (Ref.)	1.44 (1.10, 1.89)
Model 2	1 (Ref.)	0.91 (0.69, 1.20)	1 (Ref.)	1.08 (0.84, 1.40)	1 (Ref.)	1.09 (0.84, 1.40)	1 (Ref.)	0.96 (0.72, 1.29)	1 (Ref.)	1.43 (1.09, 1.87)

IQR: interquartile range; WC: waist circumference; HDL-C: high density lipoprotein-cholesterol.

* Mean (SD) age at assessment=55.1 (2.9) years

† Mean (SD) age at assessment=65.0 (1.5) years

‡ Mean (SD) age at assessment=73.9 (1.9) years

§ Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)

|| Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

Table S4. Association between the number of MetS components at <60, 60 to <70, and ≥70 years and incidence of dementia using inverse probability weighting to account for missing data.

Number of components	N Dementia cases/ Total	Rate of dementia/ 1000 person-years	HR (95% CI)		HR (95% CI) per component increment	
			Model 1 [§]	Model 2	Model 1 [§]	Model 2
At age <60 years*, Median (IQR) follow-up 20.8 (15.5, 26.2) years						
0	97/2325	2.21	1 (Ref.)	1 (Ref.)		
1	123/2145	2.93	1.26 (0.96, 1.65)	1.21 (0.93, 1.59)		
2	92/1493	3.27	1.52 (1.14, 2.03)	1.44 (1.08, 1.92)		
3	47/823	3.00	1.31 (0.93, 1.86)	1.24 (0.87, 1.76)	1.14 (1.06, 1.23)	1.12 (1.04, 1.21)
4	28/380	4.21	1.91 (1.26, 2.90)	1.84 (1.21, 2.79)		
5	6/99	3.67	1.89 (0.79, 4.50)	1.72 (0.70, 4.24)		
At age 60 to <70 years[†], Median (IQR) follow-up 10.4 (6.4, 15.6) years						
0	75/1409	4.66	1 (Ref.)	1 (Ref.)		
1	127/1753	6.31	1.32 (0.98, 1.78)	1.30 (0.97, 1.76)		
2	100/1387	6.20	1.38 (1.01, 1.89)	1.34 (0.98, 1.83)		
3	68/1089	6.32	1.50 (1.07, 2.11)	1.43 (1.02, 2.01)	1.09 (1.02, 1.17)	1.07 (1.00, 1.15)
4	33/696	5.05	1.40 (0.91, 2.14)	1.29 (0.84, 1.98)		
5	14/326	5.38	1.68 (0.94, 3.01)	1.56 (0.87, 2.80)		
At age ≥70 years[‡], Median (IQR) follow-up 4.2 (3.1, 7.1) years						
0	23/442	10.25	1 (Ref.)	1 (Ref.)		
1	57/729	15.27	1.49 (0.90, 2.46)	1.43 (0.86, 2.36)		
2	48/650	14.12	1.42 (0.86, 2.37)	1.37 (0.82, 2.29)		
3	68/844	16.10	1.56 (0.96, 2.54)	1.49 (0.91, 2.43)	1.05 (0.97, 1.15)	1.04 (0.96, 1.13)
4	50/683	16.44	1.63 (0.96, 2.76)	1.56 (0.93, 2.64)		
5	18/260	13.59	1.33 (0.71, 2.50)	1.21 (0.64, 2.29)		

IQR: interquartile range; * Mean (SD) age at assessment=55.1 (2.9) years

[†] Mean (SD) age at assessment=65.0 (1.5) years

[‡] Mean (SD) age at assessment=73.9 (1.9) years

[§] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)

^{||} Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

Table S5. Alternate cut-off points to define metabolic risk at <60, 60 to <70, and ≥70 years and incidence of dementia using inverse probability weighting to account for missing data.

Metabolic risk	Dementia cases/total, No	Rate of dementia/ 1000 person-years	HR (95% CI)	
			Model 1 [§]	Model 2
High defined as presence of ≥1 MetS components				
At age <60 years*				
No risk	97/2325	2.21	1 (Ref.)	1 (Ref.)
High risk	296/4940	3.15	1.40 (1.11, 1.76)	1.33 (1.06, 1.68)
At age 60 to <70 years[†]				
No risk	75/1409	4.66	1 (Ref.)	1 (Ref.)
High risk	342/5251	6.09	1.39 (1.07, 1.81)	1.34 (1.04, 1.75)
At age ≥70 years[‡]				
No risk	23/442	10.25	1 (Ref.)	1 (Ref.)
High risk	241/3166	15.35	1.51 (0.97, 2.35)	1.44 (0.92, 2.25)
High metabolic risk defined as presence of ≥2 MetS components				
At age <60 years*				
No risk	220/4470	2.56	1 (Ref.)	1 (Ref.)
High risk	173/2795	3.32	1.34 (1.10, 1.64)	1.29 (1.06, 1.58)
At age 60 to <70 years[†]				
No risk	202/3162	5.59	1 (Ref.)	1 (Ref.)
High risk	215/3498	5.97	1.21 (0.99, 1.48)	1.17 (0.96, 1.43)
At age ≥70 years[‡]				
No risk	80/1171	13.40	1 (Ref.)	1 (Ref.)
High risk	184/2437	15.37	1.16 (0.88, 1.53)	1.14 (0.86, 1.49)
High metabolic risk defined as presence of ≥3 MetS components (current clinical MetS definition)				
At age <60 years*				
No risk (non-MetS)	312/5963	2.73	1 (Ref.)	1 (Ref.)
High risk (MetS)	81/1302	3.39	1.23 (0.96, 1.58)	1.20 (0.94, 1.53)
At age 60 to <70 years[†]				
No risk (non-MetS)	302/4549	5.78	1 (Ref.)	1 (Ref.)
High risk (MetS)	115/2111	5.80	1.19 (0.96, 1.49)	1.14 (0.91, 1.42)
At age ≥70 years[‡]				
No risk (non-MetS)	128/1821	13.66	1 (Ref.)	1 (Ref.)
High risk (MetS)	136/1787	15.83	1.15 (0.89, 1.48)	1.13 (0.87, 1.45)

MetS: Metabolic syndrome.

* Mean (SD) age at assessment=55.1 (2.9) years; median (IQR) follow-up 20.8 (15.5, 26.2) years

† Mean (SD) age at assessment=65.0 (1.5) years; median (IQR) follow-up 10.4 (6.4, 15.6) years

‡ Mean (SD) age at assessment=73.9 (1.9) years; median (IQR) follow-up 4.2 (3.1, 7.1) years

§ Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)

|| Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

Figure S1. Flow chart of sample selection.

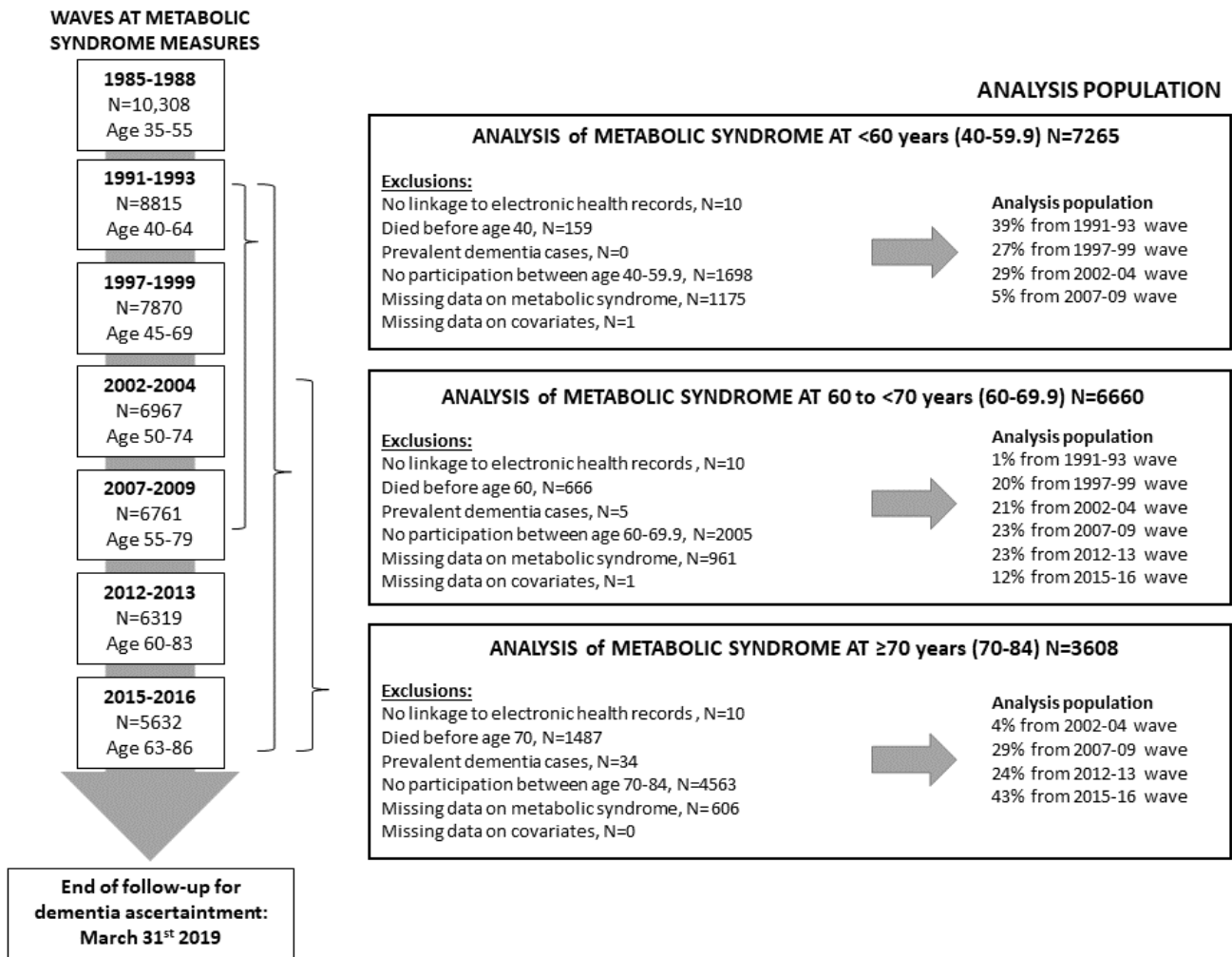
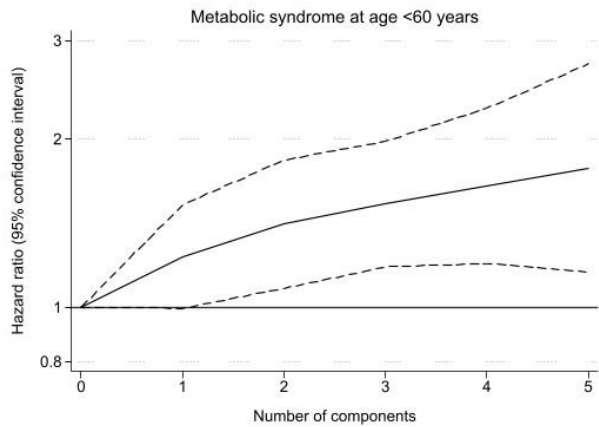
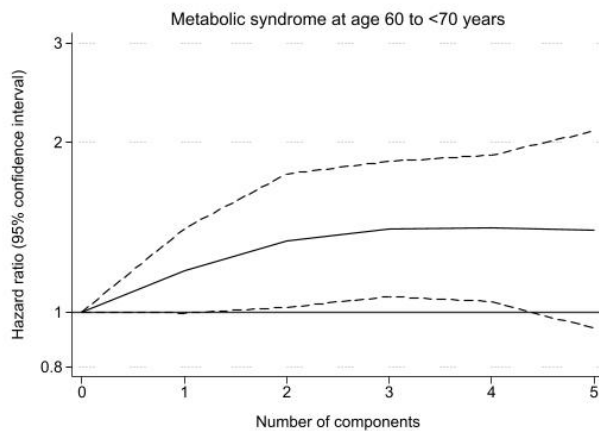


Figure S2. Association of number of metabolic syndrome components at age <60 (A), 60 to <70 (B), and ≥ 70 years (C) with dementia using restricted cubic splines.

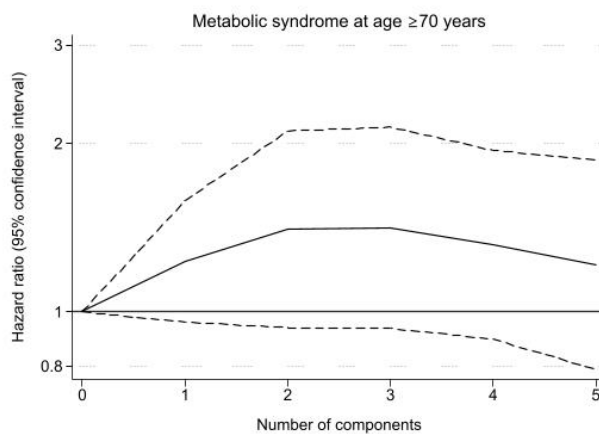
A



B



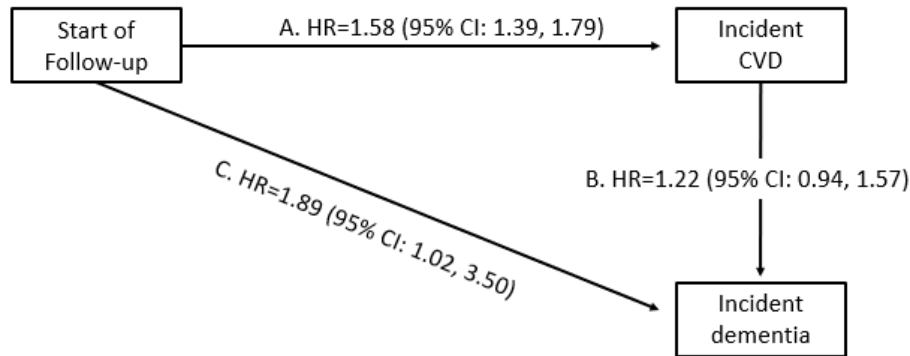
C



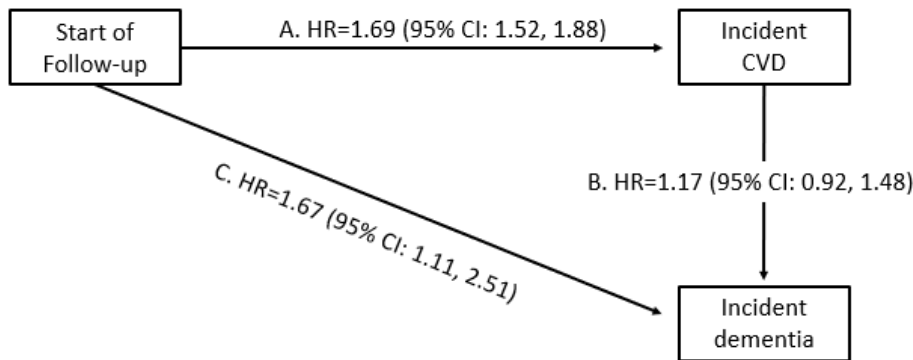
Number of metabolic syndrome components were modeled by restricted cubic splines with three age-specific knots in a Cox regression model adjusted for sex, education, ethnicity, and health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity). Hazard ratios were calculated with no metabolic syndrome components as the reference.

Figure S3. Multistate models to examine the role of “high metabolic risk” at age <60 years in transition to cardiovascular disease (stroke, coronary heart disease or heart failure) and dementia using inverse probability weighting to account for missing data.

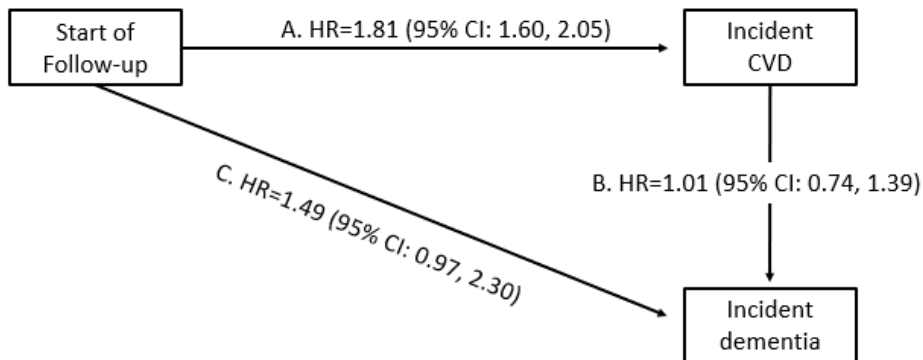
1) “High metabolic risk” at age <60 years defined as presence of ≥ 1 MetS components



2) “High metabolic risk” at age <60 years defined as presence of ≥ 2 MetS components



3) “High metabolic risk” at age <60 years defined as presence of ≥ 3 MetS components (current clinical MetS definition)



Role of “high metabolic risk” (defined as presence of ≥ 1 , ≥ 2 , or ≥ 3 MetS components) at age <60 years in the risk of transition from: A) “high metabolic risk” and CVD, B) CVD to dementia, and c) “high metabolic risk” to dementia in those free of CVD over the follow-up. Analyses with age as timescale and adjusted for sex, education, ethnicity, and health-related behaviors at age <60 (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)