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Non-diabetic Glucometabolic Statusand Progression of Aortic Stiffness: theWhitehall II study

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Materials
Supplementary statistical analyses
Distributions of glycaemic indices among non-diabetics were categorised in sex-specific quintiles and also expressed in standardised units. Linear mixed models were used to estimate the relation of the glycaemic indices with cfPWV in 2008-09 and change in cfPWV between 2008-09 and 2012-13. These models use all available cfPWV data, including where only one cfPWV measurement is available, which reduces selection bias and allows better estimates of the associations of potential confounding factors. The models also account for correlation between repeated measures within individuals. We fitted the intercept and slope with time as random effects for individual differences in cfPWV at baseline and rate of change over follow-up. From these models, the effect of each glycaemic index on cfPWV at baseline (2008-2009) is estimated by the coefficient for the main effect of the glycaemic index and the effect on progression of cfPWV between 2008-09 and 2012-13 is estimated by the interaction of the main effect with time. The longitudinal effects of the glycaemic indices have been expressed as 5-year changes in cfPWV to allow direct comparisons with other studies (refs). All estimates were initially adjusted for age, sex, ethnic group, heart rate and MAP at the time of cfPWV measurement. Baseline cfPWV and progression of cfPWV per 5 years were estimated from these models by quintile of each glycaemic index distribution and per 1SD increment in each index. This allowed us to examine associations with cfPWV across the distribution of each glycaemic index and whether the coefficients increased linearly across quintiles. Two further models cumulatively adjusted for: (i) systolic blood pressure, antihypertensive medication, lipid lowering medication, prevalent MI or stroke,smoking status andmean triglyceride and HDL-cholesterol between 2003-04 and 2008-09 and (ii) mean BMI between 2003-04 and 2008-09.

Supplementary Table S1. Characteristics of participants according to whether cfPWV was assessed

Time of assessment	Characteristic	cfPWV measured		cfPWV not measured	
		Mean (SD)	%	Mean (SD)	%
Baseline (2008-2009)	Number of participants	4347		1878	
	Age, y	65.3 (5.7)		66.0 (5.9)	
	Female		25.5		35.7
	Ethnic group: White		92.2		92.1
	South Asian		4.5		4.9
	Black		2.5		2.6
	Other		0.8		0.5
	Diabetes		14.3		19.7
	MI or stroke		5.3		8.9
	Anti-hypertensive medication		32.8		45.2
	Lipid lowering medication		30.7		39.8
	Ex-smoker		46.1		47.3
	Current smoker		4.9		7.0
Follow-up (2012-2013)	Number of participants	4485		1175	
	Age, y	69.2 (5.7)		71.0 (6.1)	
	Female		26.1		35.9
	Ethnic group: White		92.6		92.5
	South Asian		4.2		4.4
	Black		2.4		2.3
	Other		0.7		0.9
	Diabetes		12.9		21.5
	MI or stroke		5.3		8.9
	Anti-hypertensive medication		40.2		54.9

Lipid lowering medication	40.5	45.4
Ex-smoker	49.9	52.0
Current smoker	3.2	4.2

Supplementary Table S2. Descriptive statistics of characteristics that were averaged across pre-baseline (2003-2004) and baseline (2008-2009) phases in the analysisand inflammatory markers measured at pre-baseline, among the 4386 participants who contributed to the analyses

Characteristic	Average of (2003-2004) and (2008-2009)	Pre-baseline (2003-2004)	Baseline (2008-2009)
	Mean (SD)	Mean (SD)	Mean (SD)
Body mass index, kg/m^2	26.2 (3.9)	26.1 (3.9)	26.2 (4.0)
HDL cholesterol, mmol/L	1.62 (0.43)	1.60 (0.44)	1.63 (0.45)
Triglyceride, mmol/L	1.23 (0.66)	1.29 (0.79)	1.17 (0.65)
IL6, ng/ml	-	1.77*(0.57)	-
CRP, mg/L	-	1.17* (1.08)	-
Fasting glucose, mmol/L	5.13* (0.08)	5.19* (0.09)	5.07* (0.10)
2-hour glucose, mmol/L	6.14* (0.22)	5.94* (0.25)	6.23* (0.26)
HbA1c, %	5.39* (0.06)	5.16* (0.07)	5.58* (0.07)
HbA1c, mmol/mol	35.4* (0.06)	32.9* (0.07)	37.5* (0.07)
HOMA-IR	1.53* (0.62)	1.57* (0.65)	1.40* (0.68)

* Geometric mean and SD of logged values

Supplementary Table S3. The associations of glucometabolicindices with cfPWV in men and women

Glucometabolic measure[a]	Sex	cfPWV at baseline		Change in cfPWV (per 5 years)	
		Difference[b] (95% CI)	P-value	Increase[b] (95% CI)	P-value
Fasting glucose	Men	0.07 (0.01, 0.13)	0.03	0.03 (-0.06, 0.11)	0.56
	Women	0.13 (0.02, 0.25)	0.03	-0.08 (-0.23, 0.07)	0.28
	P-value for difference	0.50		0.29	
2-hour glucose	Men	0.09 (0.03, 0.15)	0.006	0.08 (-0.01, 0.17)	0.08
	Women	0.17 (0.06, 0.27)	0.002	0.05 (-0.09, 0.18)	0.52
	P-value for difference	0.29		0.80	
HbA1c	Men	0.03 (-0.03, 0.10)	0.29	0.12 (0.04, 0.21)	0.006
	Women	0.11 (0.00, 0.22)	0.04	0.10 (-0.04, 0.23)	0.17
	P-value for difference	0.24		0.81	
HOMA-IR	Men	0.13 (0.07, 0.19)	<0.001	0.12 (0.03, 0.21)	0.009
	Women	0.22 (0.11, 0.33)	<0.001	0.08 (-0.06, 0.22)	0.02
	P-value for difference	0.29		0.84	

[a] Values are the averages of measurements made at 2003-04 and 2008-09.
[b]Differences and increases in cfPWV are per 1SD change in glucometabolicmeasure and are adjusted for age, ethnic group, heart rate and mean arterial pressure at the time of the cfPWV measurement

Supplementary Table S4. The associations of glucometabolicindices with cfPWV at baseline (2008-2009)

Glucometabolic measure [a]	Model 1 [b]		Model 2 [c]		Model 3 [d]	
	Difference (95% CI)	P-value	Difference (95% CI)	P-value	Difference (95% CI)	P-value
Fasting glucose						
Q1 - lowest quintile	Ref	-	Ref	-	Ref	-
Q2	0.04 (-0.13, 0.21)	0.64	0.04 (-0.12, 0.20)	0.62	0.04 (-0.13, 0.20)	0.64
Q3	0.11 (-0.05, 0.27)	0.18	0.08 (-0.08, 0.23)	0.33	0.07 (-0.08, 0.23)	0.37
Q4	0.22 (0.06, 0.37)	0.007	0.17 (0.02, 0.33)	0.03	0.17 (0.01, 0.32)	0.03
Q5 - highest quintile	0.27 (0.11, 0.43)	0.001	0.18 (0.02, 0.34)	0.003	0.18 (0.02, 0.34)	0.03
Heterogeneity (P-value)	0.005		0.10		0.12	
2-hour glucose						
Q1 - lowest quintile	Ref	-	Ref	-	Ref	-
Q2	0.11 (-0.05, 0.27)	0.18	0.07 (-0.09, 0.23)	0.38	0.07 (-0.09, 0.23)	0.40
Q3	0.17 (0.00, 0.33)	0.05	0.09 (-0.07, 0.25)	0.29	0.08 (-0.08, 0.25)	0.31
Q4	0.10 (-0.06, 0.26)	0.22	0.00 (-0.16, 0.17)	0.96	0.00 (-0.17, 0.16)	0.97
Q5 - highest quintile	0.32 (0.15, 0.48)	<0.001	0.17 (0.00, 0.34)	0.04	0.17 (0.00, 0.34)	0.05
Heterogeneity (P-value)	0.006		0.34		0.44	
HbA1c						
Q1 - lowest quintile	Ref	-	Ref	-	Ref	-
Q2	-0.08 (-0.25, 0.09)	0.33	-0.08 (-0.25, 0.08)	0.33	-0.09 (-0.25, 0.08)	0.31
Q3	0.04 (-0.11, 0.19)	0.60	0.04 (-0.11, 0.18)	0.64	0.03 (-0.11, 0.18)	0.65
Q4	0.21 (0.04, 0.37)	0.01	0.17 (0.01, 0.33)	0.04	0.17 (0.01, 0.33)	0.04
Q5 - highest quintile	0.19 (0.02, 0.36)	0.03	0.14 (-0.02, 0.31)	0.09	0.14 (-0.03, 0.31)	0.11
Heterogeneity (P-value)	0.003		0.02		0.02	
HOMA insulin resistance						

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Q1 - lowest quintile	Ref	-	Ref	-	Ref	-
Q2	0.03 (-0.12, 0.19)	0.67	-0.02 (-0.18, 0.13)	0.76	-0.03 (-0.19, 0.13)	0.74
Q3	0.26 (0.10, 0.41)	0.002	0.13 (-0.03, 0.30)	0.10	0.13 (-0.03, 0.30)	0.12
Q4	0.35 (0.19, 0.51)	<0.001	0.17 (0.00, 0.34)	0.05	0.17 (-0.01, 0.34)	0.07
Q5 - highest quintile	0.40 (0.23, 0.57)	<0.001	0.17 (-0.01, 0.36)	0.07	0.17 (-0.04, 0.37)	0.11
Heterogeneity (P-value)	<0.001		0.07		0.11	

[a] Values are the averages of measurements made at 2003-04 and 2008-09.

[b] Model 1 is adjusted for age, sex, ethnic group, heart rate and mean arterial pressure at the time of the cfPWV measurement

[c] Model 2 is adjusted as for Model 1 + systolic blood pressure, antihypertensive medication, lipid lowering medication, prevalent MI or stroke, smoking status and mean triglyceride and HDL-cholesterol between 2003-04 and 2008-09

[d] Model 3 is adjusted as for Model 2 + mean BMI between 2003-04 and 2008-09

Supplementary Table S5. The associations of glucometabolicindices with progression of cfPWV per 5 years

Glucometabolic measure[a]	Model 1[b]		Model 2[c]		Model 3[d]	
	Difference (95% CI)	P-value	Difference (95% CI)	P-value	Difference (95% CI)	P-value
Fasting glucose						
Q1 - lowest quintile	Ref	-	Ref	-	Ref	-
Q2	0.02 (-0.21, 0.25)	0.89	-0.01 (-0.23, 0.22)	0.95	-0.03 (-0.25, 0.20)	0.81
Q3	0.01 (-0.20, 0.23)	0.91	0.01 (-0.21, 0.22)	0.96	-0.02 (-0.23, 0.19)	0.84
Q4	0.00 (-0.21, 0.22)	0.99	-0.01 (-0.23, 0.20)	0.89	-0.07 (-0.28, 0.15)	0.55
Q5 - highest quintile	0.02 (-0.20, 0.24)	0.87	-0.02 (-0.24, 0.20)	0.93	-0.08 (-0.30, 0.14)	0.46
Heterogeneity (P-value)	1.0		1.0		0.95	
2-hour glucose						
Q1 - lowest quintile	Ref	-	Ref	-	Ref	-
Q2	0.00 (-0.22, 0.21)	0.97	-0.03 (-0.25, 0.18)	0.77	-0.05 (-0.26, 0.17)	0.67
Q3	-0.01 (-0.24, 0.21)	0.90	-0.07 (-0.28, 0.15)	0.56	-0.08 (-0.30, 0.13)	0.45
Q4	0.03 (-0.19, 0.26)	0.76	0.03 (-0.19, 0.25)	0.78	-0.02 (-0.24, 0.21)	0.89
Q5 - highest quintile	0.20 (-0.03, 0.43)	0.09	0.16 (-0.07, 0.39)	0.16	0.13 (-0.10, 0.36)	0.27
Heterogeneity (P-value)	0.36		0.23		0.23	
HbA1c						
Q1 - lowest quintile	Ref		Ref			
Q2	0.14 (-0.09, 0.37)	0.24	0.13 (-0.10, 0.36)	0.27	0.12 (-0.10, 0.35)	0.29
Q3	0.05 (-0.15, 0.26)	0.62	0.06 (-0.14, 0.26)	0.58	0.06 (-0.14, 0.26)	0.58
Q4	0.11 (-0.11, 0.33)	0.34	0.10 (-0.12, 0.32)	0.39	0.09 (-0.13, 0.31)	0.44
Q5 - highest quintile	0.39 (0.15, 0.62)	0.001	0.37 (0.14, 0.60)	0.001	0.33 (0.11, 0.56)	0.004
Heterogeneity (P-value)	0.01		0.02		0.05	
HOMA insulin resistance						
Q1 - lowest quintile	Ref	-	Ref	-	Ref	-
Q2	0.06 (-0.16, 0.27)	0.61	0.03 (-0.18, 0.24)	0.76	-0.02 (-0.23, 0.20)	0.87
Q3	0.19 (-0.03, 0.40)	0.09	0.14 (-0.08, 0.36)	0.21	0.06 (-0.17, 0.28)	0.62

Q4	0.20 (-0.02, 0.42)	0.07	0.17 (-0.06, 0.39)	0.15	0.05 (-0.19, 0.29)	0.68
Q5 - highest quintile	0.39 (0.15, 0.62)	0.001	0.34 (0.09, 0.59)	0.007	0.16 (-0.12, 0.43)	0.26
Heterogeneity (P-value)	0.01		0.07		0.74	

[a] Values are the averages of measurements made at 2003-04 and 2008-09.
[b] Model 1 is adjusted for age, sex, ethnic group, heart rate and mean arterial pressure at the time of the cfPWV measurement
[c] Model 2 is adjusted as for Model 1 + systolic blood pressure, antihypertensive medication, lipid lowering medication, prevalent MI or stroke, smoking status and mean triglyceride and HDL-cholesterol between 2003-04 and 2008-09
[d] Model 3 is adjusted as for Model 2 + mean BMI between 2003-04 and 2008-09

Supplementary Table S6. The associations of glucometabolicindices measured in 2008-09 with cfPWV and progression of cfPWV

Glucometabolic measure[a]	Model adjustments	cfPWV at baseline		Change in cfPWV (per 5 years)	
		Difference[b] (95% CI)	P-value	Increase[b] (95% CI)	P-value
Fasting glucose	Model 1[c]	0.08 (0.03, 0.14)	0.002	-0.01 (-0.08, 0.06)	0.76
	Model 2[d]	0.06 (0.00, 0.11)	0.03	-0.02 (-0.09, 0.05)	0.55
	Model 3[e]	0.05 (0.00, 0.11)	0.04	-0.04 (-0.11, 0.03)	0.29
2-hour glucose	Model 1[c]	0.07 (0.02, 0.13)	0.01	0.08 (0.01, 0.15)	0.03
	Model 2[d]	0.02 (-0.03, 0.08)	0.47	0.06 (-0.01, 0.14)	0.09
	Model 3[e]	0.02 (-0.04, 0.07)	0.51	0.05 (-0.02, 0.13)	0.17
HbA1c	Model 1[c]	0.05 (-0.01, 0.10)	0.08	0.09 (0.02, 0.16)	0.01
	Model 2[d]	0.03 (-0.02, 0.08)	0.29	0.09 (0.01, 0.16)	0.02
	Model 3[e]	0.03 (-0.03, 0.08)	0.34	0.07 (0.00, 0.15)	0.04
HOMA-IR	Model 1[c]	0.17 (0.11, 0.22)	<0.001	0.11 (0.03, 0.18)	0.005
	Model 2[d]	0.09 (0.02, 0.15)	0.006	0.10 (0.02, 0.18)	0.02
	Model 3[e]	0.09 (0.02, 0.15)	0.01	0.03 (-0.06, 0.12)	0.47

[a] Values are measurements made at 2008-09.

[b]Differences and increases in cfPWV are per 1SD higher value for each glucometabolic measure

[c]Model 1 is adjusted for age, sex, ethnic group, heart rate and mean arterial pressure at the time of the cfPWV measurement

[d]Model 2 is adjusted as for Model 1 + systolic blood pressure, antihypertensive medication, lipid lowering medication, prevalent MI or stroke, smoking status and triglyceride and HDL-cholesterol values at 2008-09

[e]Model 3 is adjusted as for Model 2 + BMI at 2008-09

Supplementary Table S7. The associations of glucometabolicindices measured in 2003-04 with cfPWV and progression of cfPWV

Glucometabolicmeasure[a]	Model adjustments	cfPWV at baseline		Change in cfPWV (per 5 years)	
		Difference[b] (95% CI)	P-value	Increase[b] (95% CI)	P-value
Fasting glucose	Model 1[c]	0.07 (0.01, 0.12)	0.02	0.03 (-0.04, 0.10)	0.40
	Model 2[d]	0.04 (-0.01, 0.09)	0.15	0.03 (-0.04, 0.10)	0.42
	Model 3[e]	0.04 (-0.02, 0.09)	0.20	0.01 (-0.07, 0.08)	0.86
2-hour glucose	Model 1[c]	0.12 (0.06, 0.18)	<0.001	0.02 (-0.06, 0.09)	0.70
	Model 2[d]	0.08 (0.02, 0.14)	0.007	0.01 (-0.07, 0.08)	0.86
	Model 3[e]	0.08 (0.02, 0.14)	0.008	-0.01 (-0.08, 0.07)	0.88
HbA1c	Model 1[c]	0.09 (0.03, 0.15)	0.002	0.06 (-0.02, 0.13)	0.13
	Model 2[d]	0.07 (0.02, 0.13)	0.01	0.06 (-0.02, 0.13)	0.14
	Model 3[e]	0.07 (0.01, 0.12)	0.02	0.04 (-0.03, 0.12)	0.24
HOMA-IR	Model 1[c]	0.13 (0.07, 0.18)	<0.001	0.10 (0.03, 0.18)	0.007
	Model 2[d]	0.06 (0.00, 0.12)	0.06	0.09 (0.01, 0.17)	0.02
	Model 3[e]	0.05 (-0.02, 0.11)	0.15	0.03 (-0.05, 0.12)	0.42

[a] Values are measurements made at 2003-04.

[b] Differences and increases in cfPWV are per 1SD higher value for each glucometabolic measure

[c] Model 1 is adjusted for age, sex, ethnic group, heart rate and mean arterial pressure at the time of the cfPWV measurement

[d] Model 2 is adjusted as for Model 1 + systolic blood pressure, antihypertensive medication, lipid lowering medication, prevalent MI or stroke, smoking status and triglyceride and HDL-cholesterol values at 2008-09

[e] Model 3 is adjusted as for Model 2 + BMI at 2008-09

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Supplementary Table S8. Comparison of the association between hypertension and HbA1c in those with and without cfPWV assessment.

| Time of assessment | cfPWV status | Hypertensive status[a] | | % Difference[c] in HbA1c (95%CI) |
		Non-hypertensive Mean[b] HbA1c (95%CI)	Hypertensive Mean[b] HbA1c (95%CI)	
Baseline (2008-2009)				
	Measured	5.62 (5.60, 5.64)	5.76 (5.74, 5.79)	2.4 (1.9, 3.0)
	Not measured	5.74 (5.70, 5.79)	5.95 (5.91, 5.99)	3.6 (2.5, 4.7)
Follow-up (2012-2013)				
	Measured	5.70 (5.68, 5.72)	5.87 (5.84, 5.89)	2.9 (2.3, 3.5)
	Not measured	5.82 (5.75, 5.89)	6.01 (5.96, 6.06)	3.3 (1.7, 4.8)

[a] Hypertensive status defined as systolic BP≥140 or diastolic BP≥90 or on antihypertensive medication
[b] Means are adjusted for age, sex and ethnicity
[c] Difference in mean HbA1c in hypertensive group versus non-hypertensive group expressed as a percentage of mean in the non-hypertensive group