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ARTICLE

Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British Women's Heart Health Study

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Abstract
Aims/hypothesis Type 2 diabetes is associated with greater relative risk of CHD in women than in men, which is not fully explained by conventional cardiovascular risk factors. We assessed whether cardiovascular risk factors including more novel factors such as markers of insulin resistance, inflammation, activated coagulation and endothelial dysfunction differ more between diabetic and non-diabetic women than between diabetic and non-diabetic men, and the role of insulin resistance.
Methods A cross-sectional study of non-diabetic and diabetic men and women (n=7,529) aged 60–79 years with no previous myocardial infarction who underwent an examination was conducted. Measurements of anthropometry, blood pressure and fasting measurements of lipids, insulin, glucose and haemostatic and inflammatory markers were taken.
Results Non-diabetic women tended to have more favourable risk factors and were less insulin resistant than non-diabetic men, but this was diminished in the diabetic state. Levels of waist circumference, BMI, von Willebrand factor (VWF), WBC count, insulin resistance (HOMA-IR), diastolic blood pressure, HDL-cholesterol, tissue plasminogen activator (t-PA) and factor VIII differed more between diabetic and non-diabetic women than between diabetic and non-diabetic men (test for diabetes×sex interaction $p<0.05$). The more adverse effect of diabetes on these risk markers in women was associated with, and thereby largely attenuated by, insulin resistance.
Conclusions/interpretation The greater adverse influence of diabetes per se on adiposity and HOMA-IR and downstream blood pressure, lipids, endothelial dysfunction and systemic inflammation in women compared with men may contribute to their greater relative risk of coronary heart disease.

Keywords Cardiovascular risk factors · Diabetes · Insulin resistance · Sex

Abbreviations

CRP	C-reactive protein
CVD	Cardiovascular disease
FEV_1	Forced expiratory volume in 1 s
FVIII	Factor VIII
HOMA-IR	HOMA-insulin resistance
MI	Myocardial infarction

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t-PA	Tissue plasminogen activator antigen
VWF	von Willebrand factor
WBC	White blood cell
WC	Waist circumference

Introduction

Previous studies have shown that the relative risk of CHD incidence and mortality associated with type 2 diabetes compared with non-diabetes is stronger in women than in men [1, 2], and this difference is not explained by traditional risk factors such as blood pressure and dyslipidaemia [3]. Although early reports suggested that this difference was fully explained by the lower risk of CHD in women in the general population (i.e. without type 2 diabetes), rather than diabetes having an absolute greater detrimental effect in women [4], the Asia-Pacific Collaboration Study found a greater absolute effect, such that women with diabetes had a greater risk of CHD (7.7% experiencing a fatal CHD event) than men with diabetes (4.5%) [1]. Although not all studies observe greater absolute risk of CHD in female diabetic patients compared with male diabetic patients, many observe comparable absolute CHD risk or much smaller differences in absolute CHD or cardiovascular risk between male and female diabetic patients compared with sex differences among non-diabetic patients [3, 5–7]. The reason for the greater relative risk of CHD associated with diabetes in women compared with men is unclear and may be a consequence either of diabetes inducing a more adverse cardiovascular disease (CVD) risk profile in women combined with differences in treatment of CHD risk factors between men and women [8, 9], or be due to a need for women to undergo much larger metabolic perturbances to transit from non-diabetes to diabetes, i.e. in general women may have to 'travel' or 'deteriorate' more to get diabetes.

Previous studies have shown differences in lipid abnormalities to be more pronounced between diabetic and non-diabetic women than between diabetic and non-diabetic men [10–12]. However, these differences in the lipid profile appear insufficient to explain the differences in clinical risk [3]. Recent attention has turned to emerging CV risk factors including endothelial dysfunction, inflammation and fibrinolysis, which have been associated with diabetes risk [13]. Women with type 2 diabetes may be subject to even more adverse changes in coagulation, inflammation and vascular function than men [14–17]. Insulin resistance, a recognised contributor to hyperglycaemia and diabetes precedes the development of diabetes by years and has been associated with increased CVD risk including dyslipidaemia, hypertension, impaired fibrinolysis, inflammation and coagulation [18, 19]. Stronger associations have been reported between insulin resistance/the metabolic syndrome and inflammation and biomarkers of endothelial dysfunction in women [20]. However, few studies have explored sex differences in the emerging risk factor profile in type 2 diabetes, and the role adiposity measures and insulin resistance may play in sex differences in CVD risk factors in those with and without type 2 diabetes. The purpose of this study was to examine and compare the cardiovascular risk profile of diabetic and non-diabetic men and women, including conventional and novel risk markers, and to assess the role of adiposity and insulin resistance in contributing to the possible greater differences in atherogenic profile between diabetic and non-diabetic women and between diabetic and non-diabetic men.

Methods

Data from the British Regional Heart Study and the British Women's Heart and Health Study were used. The British Regional Heart study is a prospective study of CVD involving 7,735 British men drawn from general practices in 24 British towns followed from 1978 to 1980 [21]. In 1998–2000, all surviving men, now aged 60–79 years, were invited for a 20-year follow-up examination; 4,252 men (77% of survivors) attended. In 1999–2001, a parallel study of 4,286 women (60% of those invited) of the same age and drawn from 22 of the same 24 towns was established, with the addition of one more study town (Bristol) [22]. Full details of the selection of participants and measurements have been reported [22]. The study population were predominantly (>95%) described as white by examining nurses. Similar protocols for data collection were used in both studies. In both studies, nurses administered questionnaires, made physical measurements and collected fasting venous blood samples, from which serum was stored at −70°C for subsequent analysis. Men and women completed detailed questionnaires on medical history, medication and lifestyle, including cigarette smoking, alcohol consumption and physical activity. Details of measurement and classification methods for smoking status, physical activity, social class, blood pressure and blood lipids in the two cohorts have been described [21–25]. Serum insulin was measured using an ELISA assay, which does not cross-react with proinsulin. Insulin resistance was estimated according to the homeostasis model assessment (HOMA-IR) formula [26]. Fasting glucose measurements were available in 3,829 women (89%) and 4,032 men (95%). Prevalent diabetes was defined as either: (1) participant's report of a previous doctor's diagnosis of diabetes on questionnaire; (2) a previous diagnosis of diabetes in general practice records; or (3) fasting blood glucose ≥7.0 mmol/l. Pre-existing myocardial infarction (MI) was defined as a participant's

report of a previous doctor's diagnosis of MI on questionnaire or a previous diagnosis of MI in general practice records. All participants provided written informed consent to the investigation and ethics approval was provided by all relevant local research ethics committees. All men and women with pre-existing MI were excluded from the analyses to avoid potential biases because many haemostatic and inflammatory markers are raised as a consequence of having an MI [27], and many of them will be on medication to control their risk factors.

Haemostatic and inflammatory variables Blood was anticoagulated with K_2-EDTA (1.5 mg/ml) for measurement of white blood cell (WBC) count and plasma viscosity at 37°C in a semi-automated capillary viscometer (Coulter Electronics, High Wycombe, UK). Blood viscosity was calculated from plasma viscosity and microhaematocrit [19]. Blood was also anticoagulated with 0.109 mol/l trisodium citrate (9:1, vol./vol.) for measurement of clottable fibrinogen (Clauss method); as well as coagulation factors VII, VIII and IX in an MDA automated coagulometer. Plasma levels of tissue plasminogen activator antigen (t-PA) and D-dimer were measured with ELISA (Biopool AB, Umea, Sweden), as was von Willebrand factor (VWF) antigen (DAKO, High Wycombe, UK). C-reactive protein (CRP) was assayed by ultra-sensitive nephelometry (Dade Behring, Milton Keynes, UK). Interleukin-6 (IL-6) was assayed using a high-sensitivity ELISA (R & D Systems, Oxford, UK).

Anthropometric measurements Measurements included height, weight, waist and hip circumference. Subjects were measured standing in light clothing without shoes. Height was measured with a Holtain stadiometer to the last complete 0.1 cm and weight with a Soehnle digital electronic scale to the last complete 0.1 kg. BMI (weight/height^2 in kg/m^2) was calculated for each participant. Waist circumferences (WC) were measured in duplicate with an insertion tape (CMS Ltd, London, UK); hip circumference was measured at the point of maximum circumference over the buttocks. The waist measurement was taken from the midpoint between the iliac crest and the lower ribs measured at the sides.

Statistical analysis The distribution of CRP, IL-6, WBC count, blood viscosity and fibrin D-dimer were highly skewed and log transformation was used. Analysis of covariance was used to obtain adjusted mean levels according to sex and diabetes status. Adjustments were made in a stepwise manner, adjusting first for WC and then in addition for insulin resistance (HOMA-IR) to assess whether adiposity and insulin resistance explained the sex differences. Although duration of diabetes was not available in women, to take into account possible differences in duration of diabetes between men and women, we also adjusted in addition for glycated haemoglobin (HbA_{1c}) as HbA_{1c} generally rises with duration. Comparisons between diabetic and non-diabetic patients were carried out separately in men and women. Test for sex × diabetes interactions in their association with cardiovascular risk factors was assessed by fitting a sex × diabetes interaction term to the multivariable models. STATA was used for statistical analyses.

Results

Table 1 shows the baseline characteristics in all men and women without pre-existing MI. Overall, men tended to have significantly higher levels of adverse CVD risk factors than women; in particular higher mean levels of systolic and diastolic blood pressure, t-PA, fibrinogen, blood viscosity and fibrin D-dimer, and lower levels of HDL-cholesterol. However, women had higher levels of BMI, blood cholesterol and LDL-cholesterol, VWF, FVIII and WBC than men. There was no strong evidence of difference in levels of triacylglycerol, glucose, HOMA-IR, CRP or IL-6 between older men and women.

Table 2 shows the age-adjusted mean levels of CVD risk factors by diabetes status in men and women separately. Non-diabetic men had significantly higher levels of systolic and diastolic blood pressure, HOMA-IR, IL-6, t-PA, fibrinogen, fibrin D-dimer, blood viscosity and lower levels of HDL-cholesterol than their female counterparts, but the magnitude of difference in these risk factors between males and females with diabetes was less marked, particularly for HOMA-IR (mean sex difference diabetic vs non-diabetic patients: −0.05 vs 0.35). The higher levels of WBC and FVIII seen overall in women were more marked in diabetic than in non-diabetic patients.

Men and women with diabetes had higher levels of WC, BMI, systolic blood pressure, triacylglycerol, fasting blood glucose, HbA_{1c}, HOMA-IR and haemostatic and inflammatory markers (except for fibrin D-dimer) and lower levels of HDL-cholesterol, cholesterol, LDL-cholesterol and lung function (forced expiratory volume in 1 s; FEV_1) compared with their non-diabetic counterparts. Diabetes was associated with higher diastolic blood pressure in women but not in men. The differences in age-adjusted mean WC, BMI, blood pressure, HDL-cholesterol, triacylglycerol, HOMA, CRP, WBC, t-PA, blood viscosity and factor VIII between diabetic and non-diabetic women was greater than between diabetic and non-diabetic men. There was strong statistical evidence for sex heterogeneity in the association of diabetes with WC, BMI,

Table 1 Characteristics and level of atherosclerotic risk factors by sex in subjects with no pre-existing MI

Characteristics and risk factors	Men n=3,752	Women n=3,777	p Value for sex difference
Age (years)	68.6±5.5	68.7±5.5	0.18
Diabetes % (n)	11.1 (416)	9.5 (360)	0.03
Current smokers, % (n)	13.0 (486)	10.9 (411)	0.006
Alcohol drinkers (daily/most days), % (n)	36.1 (1,354)	17.1 (647)	<0.001
Statins, % (n)	3.9 (145)	5.8 (220)	<0.001
Antihypertensive drugs, % (n)	24.0 (911)	29.0 (1,092)	<0.001
WC (cm)	97.1±10.4	86.1±12.1	<0.001
BMI (kg/m^2)	26.9±3.7	27.5±4.9	<0.001
SBP (mmHg)	150.0±24.0	147.2±25.1	<0.001
DBP (mmHg)	85.6±11.0	79.5±11.6	<0.001
HDL-cholesterol (mmol/l)	1.33±0.34	1.67±0.45	<0.001
LDL-cholesterol (mmol/l)	3.91±0.95	4.16±1.08	<0.001
Cholesterol (mmol/l)	6.04±1.06	6.66±1.20	<0.001
Triacylglycerol (mmol/l)[a]	1.62 (1.15, 2.2)	1.66 (1.2, 2.2)	0.07
HOMA[a]	2.00 (1.39, 3.14)	1.81 (1.12, 2.62)	<0.001
Fasting glucose (mmol/l)[a]	5.84 (5.25, 6.09)	5.92 (5.4, 6.2)	0.020
HbA_{1c} (%)	5.01±0.92	4.99±0.86	0.42
HbA_{1c} (mmol/l)	31.22±10.02	31.04±9.43	0.42
FEV_1 (l/l)	2.61±0.66	1.98±0.48	<0.001
Haemostatic and inflammatory markers			
CRP (mg/l)[a]	1.70 (0.81, 3.40)	1.76 (0.83, 3.94)	0.23
WBC (10^9/l)[a]	6.80 (5.7, 8.0)	6.96 (0.59, 8.3)	<0.001
IL-6 (pg/ml)[a]	2.41 (1.55, 3.42)	2.33 (1.49, 3.32)	0.02
Fibrinogen (g/l)	3.25±0.73	3.44±0.70	<0.001
t-PA (ng/ml)[a]	10.1 (7.7, 13.4)	8.00 (6.1, 10.9)	<0.001
Fibrin D-dimer (ng/ml)[a]	81.3 (48, 123)	89.1 (54, 142)	<0.001
Blood viscosity (mPa×s)[a]	4.21 (3.89, 4.53)	3.97 (3.67, 4.27)	<0.001
Factor VIII (IU/l)	1,317±319	1,600±378	<0.001
VWF (IU/l)	1,385±462	1,473±470	<0.001

Data are mean±SD except as indicated

DBP, diastolic blood pressure; SBP, systolic blood pressure

[a]Geometric mean (interquartile range)

diastolic blood pressure, HDL-cholesterol, HOMA-IR, t-PA and FVIII (test for diabetes×sex interaction all p values <0.05) and some evidence for blood viscosity (p=0.06). There was little statistical evidence for heterogeneity between men and women for diabetes risk factor associations for CRP, systolic blood pressure and triacylglycerols despite the point estimates for the associations with these risk factors being greater in females as with other risk factors. Exclusion of men and women on statins made little difference to the findings seen in Table 2.

The diabetes×sex interactions seen for diastolic blood pressure, HOMA, t-PA, WBC and FVIII changed little with adjustment for differences in WC, but were attenuated after further adjustment for HOMA-IR (Table 3). The diabetes×sex interaction for the association with WBC remained even after these adjustments. Adjustment for HOMA-IR reversed the positive association between diabetes and t-PA, which became inverse after adjustment for HOMA-IR in both sexes.

Glycated haemoglobin levels (HbA_{1c}) were similar in diabetic men and diabetic women and adjustment for HbA_{1c} had little effect on the above findings.

Discussion

Men have much higher absolute risk of CHD than women, although the gap narrows after the menopause. The majority of studies have shown that the relative risk of CHD associated with diabetes is far greater in women than in men [1, 2], resulting in comparable or smaller sex differences in absolute CHD risk in diabetic patients [3, 5–7]. The reasons why diabetes in women increases the relative risk of CHD more than in men compared with their non-diabetic counterpart is not clear, but a possible explanation may be that diabetes has a greater adverse effect on CVD risk factors in women than in men.

Table 2 Age-adjusted mean levels of biological and haemostatic and inflammatory markers in non-diabetic and diabetic men and women with no MI

Variable	Men				Women				Men vs women		
									p value difference		
	Non-diabetic	Diabetic	D–ND	*p* value[a]	Non-diabetic	Diabetic	D–ND	*p* value[a]	Non-diabetic	Diabetic	Sex×diabetes interaction
Age (years)	68.5	69.0	0.5	0.11	68.7	69.4	0.7	0.01			0.49
WC (cm)	96.6	101.3	4.7	<0.001	85.3	93.5	8.2	<0.001	<0.0001	<0.0001	<0.0001
BMI (kg/m^2)	26.7	28.2	1.5	<0.001	27.3	29.9	2.6	<0.001	<0.0001	<0.0001	0.0006
SBP (mmHg)	149.4	155.4	6.0	<0.001	146.5	153.8	7.3	<0.001	<0.0001	0.5	0.39
DBP (mmHg)	85.6	85.3	−0.3	0.54	79.3	80.7	1.4	0.03	<0.0001	<0.0001	0.02
HDL-cholesterol (mmol/l)	1.34	1.23	−0.11	<0.001	1.68	1.49	−0.19	<0.001	<0.0001	0.0001	0.006
LDL-cholesterol (mmol/l)	3.94	3.68	−0.26	<0.001	4.19	3.85	−0.34	<0.001	<0.0001	0.01	0.41
Cholesterol (mmol/l)	6.06	5.92	−0.14	0.01	6.69	6.42	−2.7	<0.001	<0.0001	<0.0001	0.24
Triacylglycerol (mmol/l)[b]	1.58	2.03	0.45	<0.001	1.61	2.17	0.56	<0.001	0.1	0.06	0.15
HOMA[b]	1.94	5.93	3.99	<0.001	1.59	5.88	4.29	<0.001	<0.0001	0.96	0.0002
Fasting glucose (mmol/l)[b]	5.55	8.78	3.23	<0.001	5.68	8.64	2.96	<0.001	<0.0001	0.54	0.0004
HbA_{1c} (%)	4.84	6.31	1.47	<0.001	4.85	6.26	1.41	<0.001	0.6	0.6	0.28
HbA_{1c} (mmol/l)	29.42	45.52	16.1	<0.001	29.52	44.92	15.4	<0.001	0.6	0.6	0.28
FEV_1 (l/l)	2.62	2.52	−0.10	<0.001	1.99	1.90	−0.09	<0.001	<0.0001	<0.0001	0.60
Haemostatic and inflammatory markers											
CRP (mg/l)[b]	1.65	2.13	0.48	<0.001	1.69	2.48	0.79	<0.001	0.4	0.10	0.19
WBC (10^9/l)[b]	6.75	7.13	0.38	<0.001	6.88	7.66	0.78	<0.001	0.005	0.005	0.01
IL-6 (pg/ml)[b]	2.38	2.68	0.30	<0.001	2.29	2.69	0.4	<0.001	0.009	0.99	0.43
Fibrinogen (g/l)	3.24	3.34	0.10	0.009	3.43	3.53	0.10	0.009	<0.0001	0.002	0.95
t-PA (ng/ml)[b]	9.93	11.5	1.57	<0.001	7.81	10.1	2.29	<0.001	<0.0001	<0.001	0.0007
Fibrin D-dimer (ng/ml)[b]	81.5	79.7	−1.8	0.605	89.3	86.8	−2.5	0.547	<0.0001	0.23	0.83
Blood viscosity (mPa.s)[b]	4.20	4.30	0.10	<0.001	3.96	4.12	0.16	<0.001	<0.0001	<0.0001	0.06
Factor VIII (IU/l)	1,302	1,435	133	<0.001	1,581	1,775	194	<0.001	<0.0001	<0.0001	0.01
VWF (IU/l)	1,367	1,528	161	<0.001	1,459	1,606	147	<0.001	<0.0001	0.06	0.65

DBP, diastolic blood pressure; SBP, systolic blood pressure

[a] *p* value for difference between diabetic and non-diabetic participants (D–ND)

[b] Geometric mean

In this large study of older men and women sampled across the UK, non-diabetic women tended to have a more favourable risk profile than non-diabetic men and in particular were less insulin resistant than men but this difference was markedly diminished in the diabetic state. Contrary to findings with most CVD risk factors, women without diabetes had significantly higher levels of VWF and WBC than men without diabetes; this sex difference was more marked in women and men with diabetes. Although absolute levels were not higher, diabetic women showed greater relative differences in abdominal adiposity (WC), insulin resistance, lipids (low HDL-cholesterol), diastolic blood pressure, inflammation (WBC), endothelial dysfunction (t-PA) and coagulation (FVIII) than diabetic men when compared with their non-diabetic counterparts. The sex differences in the association between diabetes and these risk markers were to some extent explained by adiposity and more strongly by insulin resistance (HOMA-IR).

Our study supports and extends previous studies by examining the cardiovascular risk profile of a wide range of novel risk markers including markers of inflammation and

Table 3 Adjusted mean differences in biological and haemostatic and inflammatory markers between diabetic and non-diabetic participants (Diab–Non-diab) with no MI and in mean levels between men and women according to diabetes status

Variable	Men (n=3,752)		Women (n=3,777)		Non-diabetic patients	Diabetic patients	Sex × diabetes interaction
	Diab–Non-diab	p value for difference	Diab–Non-diab	p value for difference	Men–women	Men–women	
Adjusted for age and WC							
DBP (mmHg)	−0.83	0.15	1.33	0.04	6.4	4.2	0.03
HDL-cholesterol (mmol/l)	−0.07	0.0002	−0.11	<0.0001	−0.34	−0.29	0.09
Factor VIII (IU/l)	117	<0.0001	163	<0.0001	−279	−326	0.04
HOMA[a]	3.29	<0.0001	3.32	<0.0001	0.35	0.32	0.01
Fasting glucose (mmol/l)[a]	3.19	<0.0001	2.86	<0.0001	−0.13	0.20	<0.0001
WBC (10^9/l)[a]	0.31	0.002	0.59	<0.0001	−0.13	−0.41	0.03
t-PA (ng/ml)[a]	0.88	<0.0001	1.23	<0.0001	2.13	1.78	0.03
Adjusted for age, WC and HOMA							
DBP (mmHg)	−1.11	0.10	1.23	0.11	6.4	4.0	0.05
HDL-C (mmol/l)	0.05	0.008	0.02	0.50	−0.34	−0.30	0.21
Factor VIII (IU/l)	38.5	0.04	64.9	0.007	−282	−308	0.08
Fasting glucose (mmol/l)[a]	2.29	<0.0001	1.99	<0.0001	−0.12	0.18	<0.0001
WBC (10^9/l) [a]	0.13	0.26	0.40	0.001	−0.13	−0.39	0.04
t-PA (ng/ml) [a]	−0.46	0.04	−0.44	0.03	2.13	2.11	0.05

DBP, diastolic blood pressure; Men–women, difference in mean levels between men and women

[a] Geometric mean

endothelial dysfunction in non-diabetic and diabetic men and women and assessing the role of insulin resistance (HOMA-IR) in explaining these sex differences. Our findings are in keeping with the notion that as women go from non-diabetes to diabetes, they have to 'travel' further, i.e. they need to put on more weight, and deteriorate their insulin sensitivity and related risk factors to a greater extent than do men. They do so in part because the average middle-aged women (in differing parts of the world) are at lower risk of diabetes (and thus more insulin sensitive) than the average man as shown by recent studies [28].

Women with diabetes, compared with their non-diabetic counterparts, showed a greater difference in central adiposity than was seen when comparing diabetic and non-diabetic men, consistent with the finding that WC has been shown to be a stronger predictor of diabetes in women than in men [25]. The relatively greater difference between men and women in adiposity partially explains the greater difference in insulin resistance seen between diabetic women and non-diabetic women compared with men. The stronger relative association between diabetes and HDL-cholesterol and diastolic blood pressure in women than in men observed in this study has been noted in other studies [3, 9], and we have shown this to be associated with the relative greater adiposity and insulin resistance (HOMA-IR) in women. Unlike previous studies we did not find any significant interaction between diabetes status and LDL-cholesterol [11]. This difference in findings may relate to age as in this study non-diabetic women had higher (not lower as commonly seen in younger populations) LDL-cholesterol and cholesterol levels than their male counterparts [11]. Moreover, both male and female diabetic patients showed lower not higher levels of LDL-cholesterol and total cholesterol than non-diabetic patients, which was not explained by use of statins. The lower level of LDL-cholesterol in diabetic patients compared with non-diabetic patients has been observed in the Strong Heart Study [9] and is largely linked to alteration in LDL particle composition in diabetes with appearance of smaller denser particles that contain less cholesterol.

Insulin resistance has been associated with abnormalities of coagulation, inflammation, endothelial dysfunction and fibrinolysis [18, 19]. The greater relative risk of CHD associated with diabetes in women may be explained by diabetes producing a more adverse change in the coagulation, inflammation and fibrinolytic system than men [14–17]; or, as explained above, changes in such pathways are simply greater due to a greater deterioration in insulin resistance in women. We examined several markers of inflammation that have been associated with diabetes and CHD including CRP, IL-6 and WBC [13, 23], and all showed differing patterns of associations. In this older population there were no sex differences in levels of CRP in those with or those without

diabetes. Non-diabetic men showed significantly higher levels of IL-6 than non-diabetic women but this sex difference was abolished in diabetic patients. However, both non-diabetic and diabetic women showed significantly higher levels of WBC than their male counterparts and the difference was more marked in diabetic patients. A significant sex×diabetes interaction was seen for WBC, which was robust to adjustment for WC and HOMA-IR, but no sex difference was found for the association with CRP or IL-6. Sex×diabetes interactions with CRP have been observed in some but not all studies [14, 29]. Our finding of a marked sex×diabetes interaction in the association with WBC has some consistency with the finding that WBC has been shown to be more strongly correlated with insulin sensitivity in older women than in men [30].

Circulating biomarkers of endothelial dysfunction such as VWF and t-PA have been shown to predict CHD [23]. Women had significantly higher levels of VWF (one marker of endothelial dysfunction) and FVIII than men in both non-diabetic and diabetic participants; circulating factor VIII levels partly reflect levels of its endothelial-derived carrier protein, VWF (as shown by the strong correlation (0.68) between factor VIII and VWF in the present study). However, men had significantly higher levels of t-PA antigen than women in both groups but the sex difference diminished in diabetic patients. Diabetes was associated with a more adverse effect on t-PA in women than in men, which is consistent with the stronger influence of diabetes on plasminogen activator inhibitor 1 (PAI-1) in women observed in previous studies [18]. Elevated t-PA antigen (which largely reflects circulating inactive tPA–PAI-1 complexes) is considered an integral feature of the insulin resistance syndrome [19]; the greater difference in t-PA between diabetic and non-diabetic women was entirely explained by insulin resistance and WC. Thus, the greater increase in endothelial dysfunction may also contribute to the loss of cardiovascular protection in diabetic women.

Although the majority of studies have shown the relative risk of CHD associated with diabetes is far greater in women [1, 2] than in men, it is important to note that the absolute risk of CHD has not always been shown to be greater in diabetic women than in diabetic men [3, 5–7, 31]. Nevertheless many of these cohort studies have shown comparable absolute risk of coronary or cardiovascular events in diabetic women compared with diabetic men or diminished sex differences in absolute risk in the diabetic state [3, 5–7]. This is consistent with the pattern seen for many of the CVD risk factors observed in this study, where the more favourable pattern of risk factors seen in women is diminished in the diabetic state suggesting that the greater excess in CVD risk factors in diabetic women may contribute to the greater increase in relative risk of CHD in diabetic women.

The strengths and limitations of the present study require careful consideration. The study population is not strictly a random population sample, being influenced by survival and response, both of which will tend to lead to under-representation of selected groups of individuals such as smokers or obese participants. Although this may affect the average levels of the biological markers in the population, there is no reason to believe that under-representation per se should bias the relationships between diabetes and the biological markers studied. However, the average HbA_{1c} (which generally increases with duration) was near identical in diabetic women compared with diabetic men suggesting similar duration in male and female diabetic patients. We cannot extend our findings to other ethnic groups or to younger participants. The cross-sectional nature of our study cannot provide evidence as to whether development of type 2 diabetes mellitus in women exerts or requires more adverse changes in coagulation, inflammation and vascular function than in men, although this hypothesis would fit with the current data. Nor can we provide direct evidence as to whether these greater differences seen particularly for insulin resistance, HDL-cholesterol and markers of activated coagulation, inflammation and endothelium between diabetic women and non-diabetic women compared with non-diabetic men and diabetic men contribute to the greater relative risk of CHD associated with diabetes in women. Both these aspects require future study.

In conclusion, in this large study of older adults aged 60–79 years, women tended to have more favourable cardiovascular risk factors than men, but many of these advantages were diminished or abolished in the diabetic state. Diabetes was associated with increased CVD risk factors in both men and women, but diabetic women showed greater relative excess in many CVD risk factors than diabetic men; these excesses were to some or a large degree explained by the greater increase in adiposity and insulin resistance associated with diabetes in women than in men. Our results therefore are consistent with the hypothesis that women have to undergo a greater metabolic deterioration to develop diabetes than do men and as such, many insulin resistance-related risk factors, as observed herein, must change to a greater extent. The greater relative excess in many CVD risk factors in diabetic women may help to explain the increased relative risk of CHD in women with diabetes compared with men.

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carried out the statistical analysis and contributed to the drafting of the manuscript. DAL, PHW, GDL and SE contributed to the acquisition of the data, the interpretation of the data and critically revised the manuscript for important intellectual content. NS contributed to the conception and design and the drafting of the manuscript. All authors approved the final version to be published.

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References

1. Huxley R, Barzi F, Woodward M (2006) Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 332:73–78
2. Lee WL, Cape D, Cheung AM, Zinman B (2000) Impact of diabetes on coronary artery disease in women and men. A meta-analysis of prospective studies. Diabetes Care 23:962–968
3. Juutilainen A, Kortelainen S, Lehto S, Ronnemaa T, Pyorala K, Laakaso M (2004) Gender difference in the impact of type 2 diabetes on coronary heart disease risk. Diabetes Care 27:2898–2904
4. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL (1991) Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. JAMA 265:627–631
5. Natarajan S, Liao Y, Sinha D, Cao G, Lipsitz SR, McGee DL (2003) Sex differences in risk for coronary heart disease mortality associated with diabetes and established coronary heart disease. Arch Intern Med 163:1735–1740
6. Becker A, Bos G, de Vegt F et al (2003) Cardiovascular events in type 2 diabetes: comparison with nondiabetic individuals. Eur Heart J 24:1406–1413
7. Juutilainen A, Pyorala K, Lehto S, Laakso M, Ronnema T (2005) Type 2 diabetes as a "coronary heart disease equivalent": an 18 year prospective population based study in Finnish subjects. Diabetes Care 28:2901–2907
8. Wexler DJ, Nathan DM, Grant RW, Cagliero E, Meigs JB (2005) Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. Diabetes Care 28:514–520
9. Howard BV, Cowan LD, Go O, Welty TK, Robbins DC, Lee ET, Strong Heart Study Investigators (1998) Adverse effects of diabetes on multiple cardiovascular disease risk factors in women. Diabetes Care 21:1258–1265
10. Haffner SM, Miettenen H, Stern MP (1997) Prelatively more atherogenic coronary heart disease risk factors in prediabetic women than in prediabetic men. Diabetologia 40:711–717
11. Williams K, Tchernof A, Hunt KJ, Wagenknecht LE, Haffner SM, Sniderman AD (2008) Diabetes, abdominal adiposity, and atherogenic dyslipoproteinemia in women compared with men. Diabetes 57:3289–3296
12. Siegel RD, Cupples A, Schaefer EJ, Wilson PWF (1996) Lipoproteins, apolipoproteins, and low-density lipoprotein size among diabetics in the Framingham Offspring Study. Metabolism 45:1267–1271
13. Sattar N, Wannamethee SG, Forouhi NG (2008) Novel biochemical risk factors for type 2 diabetes: pathogenic insights or prediction possibilities? Diabetologia 51:926–940
14. Steinberg HO, Paradisi G, Cronin J et al (2000) Type II diabetes abrogates sex differences in endothelial function in premenopausal women. Circulation 101:2040–2046
15. Chan P (1995) Coagulation activation in type 2 diabetes mellitus: the higher coronary risk of female diabetic patients. Diabet Med 12:504–507
16. Donahue RP, Rejman K, Rafalson LB, Dmochowski J, Strange S, Trevisan M (2007) Sex differences in endothelial function markers before conversion to pre-diabetes: does the clock start ticking earlier among women: the Western New York study. Diabetes Care 30:354–359
17. Mansfield MW, Heywood DM, Grant PJ (1996) Sex differences in coagulation and fibrinolysis in white subjects with non-insulin dependent diabetes mellitus. Artherioscler Thromb Vasc Biol 16:160–164
18. Yudkin JS. Abnormalities of coagulation and fibrinolysis in insulin resistance. Evidence for a common antecedent. Diabetes Care 22 (Suppl 3):C25–C30
19. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH (2005) The metabolic syndrome and insulin resistance: relationship to haemostatic and inflammatory markers in older non-diabetic men. Atherosclerosis 181:101–108
20. Regitz-Zagrosek V, Lehmkuhl E, Weickert MO (2006) Gender differences in the metabolic syndrome and their role for cardiovascular disease. Clin Res Cardiol 95:136–147
21. Shaper AG, Pocock SJ, Walker M, Cohen NM, Wale CJ, Thomson AG (1981) British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns. BMJ 283:179–186
22. Lawlor DA, Bedford C, Taylor M, Ebrahim S (2003) Geographical variation in cardiovascular disease, risk factors, and their control in older women: British Women's Heart and Health Study. J Epidemiol Community Health 57:134–140
23. Wannamethee SG, Whincup PH, Shaper AG, Rumley A, Lennon L, Lowe GDO (2009) Circulating inflammatory and haemostatic biomarkers are associated with risk of myocardial infarction and coronary death, but not angina pectoris, in older men. J Thromb Haemost 7:1605–1611
24. Emberson J, Whincup PH, Walker M, Thomas M, Alberti KGM (2002) Biochemical measures in a population based study: the effect of fasting duration and time of day. Ann Clin Biochem 39:493–501
25. Wannamethee SG, Papacosta O, Whincup PH et al (2010) Assessing prediction of diabetes in older adults using different adiposity measures: a 7 year prospective study in 6,923 older men and women. Diabetologia 53:890–898
26. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Preacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
27. Wannamethee SG, Lowe GDO, Shaper AG, Rumley A, Lennon L, Whincup PH (2004) Insulin resistance, haemostatic and inflammatory markers and coronary heart disease risk factors in type 2 diabetes with and without coronary heart disease. Diabetologia 47:1557–1565
28. Lipscombe LL, Hux JE (2007) Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995–2005: a population-based study. Lancet 369:750–756
29. Saltevo J, Kautiainen H, Vanhala M (2009) Gender differences in adiponectin and low grade inflammation among individuals with normal glucose tolerance, prediabetes and type 2 diabetes. Gend Med 6:463–470
30. Nilsson G, Hedberg P, Jonason T, Lonnberg I, Tenerz A, Ohrvik J (2007) White blood cell counts associate more strongly to the metabolic syndrome in 75 year-old women than in men: a population based study. Metab Syndr Relat Disord 5:359–364
31. Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB (1988) Mortality among diabetics in a national sample. Am J Epidemiol 128:389–401