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Dissimilar association of conventional immuno-reactive versus specific insulin with cardiovascular risk factors: a consequence of proinsulinaemia?

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Abstract

In this study involving 365 non-diabetic elderly Caucasians, we examined the relationship of immuno-specific insulin (ISI), total immuno-reactive insulin (IRI), proinsulin (PI) and proinsulin–insulin ratio (PI:ISI) to serum high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean blood pressure (MBP) and pulse pressure. In a multiple regression analysis, adjusted for age, sex and obesity, a 1.3-fold stronger inverse association with HDL-C levels was found for IRI than for ISI, with a 1.6-fold better fit of the regression equation. The positive association of insulin with TG was 1.6-fold stronger for IRI compared to ISI, with a 2.5-fold better fit. In contrast, the positive association of IRI with the various blood pressure parameters was 1.5–1.9-fold weaker than for ISI, with a 2.1–3.8-fold worse fit. Both PI:ISI ratio and PI were independently associated with TG levels, but not with HDL-C. The PI:ISI ratio, but not PI, was associated with blood pressure, but dependent on glycaemia. In conclusion, compared to ISI, IRI overestimates the association of insulin with serum lipids and underestimates the association of insulin with blood pressure. The use of non-specific insulin assays may explain the inconsistencies in the findings of previous epidemiological studies. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Glucose tolerance; Cardiovascular risk factors; Insulin; Insulin resistance; Proinsulin

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1. Introduction

Various studies have demonstrated that insulin resistance is associated with high triglyceride and blood pressure levels, and inversely associated with glucose tolerance and serum high-density lipoprotein cholesterol (HDL-C) levels [1–3]. Insulin resistance is considered to represent the basic defect which results in the clustering of these well established cardiovascular risk factors [4], also known as syndrome X [2] or the insulin resistance syndrome (IRS) [5].

In epidemiological studies, fasting serum insulin concentrations, reflecting insulin resistance, have been examined in relation to these risk factors [6–9]. The relationship of insulin to HDL-C, and in particular TG, is well established, whereas for blood pressure no consistent relationship with serum insulin levels has yet been found [10–17]. Some studies have confirmed an association [10,11], but others have not been able to demonstrate this [12–17].

As most studies measure total immuno-reactive insulin (IRI), rather than immuno-specific insulin (ISI), these inconsistencies may, at least partly, be a consequence of confounding by circulating insulin precursor molecules. A disproportional elevation of proinsulin (PI) levels has been found in subjects with impaired glucose tolerance (IGT) [18] and non-insulin-dependent diabetes mellitus (NIDDM) [19–21]. Consequently, immuno-reactive immuno-assays may overestimate the ‘true’ biologically active insulin concentrations [22] among subjects with abnormal glucose tolerance. It is suggested that insulin-specific assays should be used as a measure of insulin resistance in epidemiological research [23]. However, evidence for substantial differences between the magnitude of the associations of IRI and ISI with various cardiovascular risk factors is still lacking [24]. Whether there is an independent relationship between cardiovascular risk factors and proinsulin, or the proinsulin–insulin ratio (PI:ISI ratio), remains to be established.

This study among non-diabetic Caucasians examines whether there are differences between ISI and IRI in relation to serum lipids and blood pressure. To determine whether cross-reactivity of

PI with the IRI assay could explain differences between ISI and IRI, we investigated whether the relationship of the sum of ISI and PI (ISI + PI) to cardiovascular risk factors is comparable to that of IRI. Our final objective was to determine whether there is an independent relationship of PI and the PI:ISI ratio to the various risk factors.

2. Materials and methods

2.1. Subjects

The source population consisted of Caucasian men and women ($n = 3553$, aged 50–74 years), randomly selected from the registry office of the medium-sized town of Hoorn in the Netherlands, which has 59000 (mixed rural and urban) inhabitants. The survey took place from October 1989 to December 1991, with a response rate of 71.5% ($n = 2540$). An oral glucose tolerance test (OGTT) was performed, according to the 1985 WHO criteria, with a 75-g glucose-equivalent load. Fasting and 2-h blood specimens were obtained, plasma and serum were separated for the immediate determination of serum lipids and plasma glucose concentrations, and serum was stored at -20°C for subsequent assessment of serum insulin and proinsulin levels.

In order to obtain a more precise assessment of glucose and (pro)insulin concentrations, the OGTT was repeated within 2–6 weeks on the same day of the week and at the same time of day as the first test. The subjects had not been informed of the results of the first test. For reasons of efficiency, all glucose-intolerant subjects ($n = 460$), and a random age- and gender-stratified sample of subjects with normal glucose tolerance ($n = 323$, five strata for both sexes: < 55 , 55–59, 60–64, 65–69 and 70–74 years; mean sample fraction: 16%), were invited for this second OGTT, with a participation rate of 92%. A detailed description of the sampling method has already been published elsewhere [25,26].

By applying the WHO criteria on mean glucose values from two oral glucose tolerance tests, 544 subjects were classified as non-diabetic. We excluded all subjects who were taking blood-pres-

sure-lowering medication ($n = 133$) or blood-lipid-lowering medication ($n = 5$), with triglyceride levels of more than 10 mmol/l (likely to be genetically determined, $n = 1$) or with missing values ($n = 40$). The final study population consisted of 186 men and 179 women, including 54 men and 62 women with IGT.

2.2. Measurements

Glucose was measured in plasma by the glucose–dehydrogenase method (Merck, Darmstadt, Germany). Glycolysated haemoglobin (HbA_{1c}) was determined by ion-exchange high-performance liquid chromatography, using a Modular Diabetes Monitoring System (Bio-Rad, Veenendaal, The Netherlands, normal range 4.3–6.1, inter-assay coefficient of variation (CV) 0.6–3.1%). Immuno-specific insulin (ISI) was measured in serum by a double-antibody radioimmunoassay (lot SP21, Linco Research, St. Louis, MO) in which proinsulin and des(31,32)proinsulin cross-react by less than 0.2%. The cross-reactivity with des(64,65)proinsulin in this assay is 76%, but this will barely contribute to the measured insulin values because des(64,65)proinsulin is only a minor component in human serum [27]. The working range of ISI, over which the inter-assay CV was less than 15%, was 25–1800 pmol/l; the CV was 6% at ISI levels in the range 40–1000 pmol/l. The lower limit of sensitivity was 12 pmol/l. Immuno-reactive insulin (IRI) was measured in serum by means of a double-antibody radioimmunoassay using Novo antibody M 8170 (Novo Nordisk, Denmark), in which proinsulin and des(31,32)proinsulin cross-react by approximately 80%. The working range of IRI, over which the inter-assay CV was less than 15%, was 40–1200 pmol/l; the CV was 6% at IRI levels in the range 100–800 pmol/l. The lower limit of sensitivity was 12 pmol/l. Proinsulin was measured by means of a double-antibody radioimmunoassay based on reagents from Dr. R. Bowsher (Lilly Laboratory for Clinical Research, Indianapolis, USA), as previously described [28]. In this assay, using the polyclonal antibody 168 AB, des(31,32)proinsulin cross-reacts by 63%, and des(64–65)proinsulin by 19%. The working range of proinsulin, over which

the inter-assay CV was less than 15%, was 20–400 pmol/l; the CV was 6% at proinsulin levels of 100 pmol/l. The lower limit of sensitivity was 3 pmol/l. All hormone measurements were performed twice. The CV values were calculated from the results of quality control samples at various levels of analytes, which were analysed in each run performed for this study. In 50 samples, the fasting proinsulin concentrations were below the detection limit of the assay. These values were considered to be positioned somewhere between zero and 3 pmol/l, and were substituted by a random value from this interval. Fasting serum lipids were based on one measurement during the first OGTT; triglyceride levels were determined by an enzymatic technique (Boehringer-Mannheim, Mannheim, Germany), and high-density lipoprotein levels were determined by a precipitation method [29].

Blood pressure was measured prior to the OGTTs on the right arm of the subjects, after at least 5 min of rest in a sitting position, with a random zero mercury sphygmomanometer (Hawksley-Gelman). We calculated the average of two readings of systolic and diastolic (Korotkoff V) blood pressure to the nearest even digit recorded each time. As an estimate of vascular resistance, mean blood pressure was calculated as follows: $MBP = [(2/3 \text{ DBP}) + (1/3 \text{ SBP})]$; as an estimate of arterial compliance (stiffness), the pulse pressure, BP_{diff} was calculated as the difference between SBP and DBP.

The height and weight of the subjects were measured without shoes and outer garments on the first visit, and body-mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Waist and hip measurements were taken, according to a standardized procedure [30], as the horizontal circumference half-way between the lower rib margin and the iliac crest, and the point of maximum circumference over the buttocks, respectively. Waist-to-hip ratio (WHR) was defined as waist circumference divided by hip circumference.

2.3. Data analysis

Apart from WHR and HDL-C, only small sex-related differences were found for the various variables with otherwise similar distributions, so

pooled data are presented to increase the statistical power, and also to simplify the presentation. Since the clearance rate of proinsulin is approximately 30% lower than that of insulin [31], we used the fasting PI:ISI ratio, assuming a steady state, and fasting insulin levels, as in epidemiological studies among non-diabetics, fasting insulin seems to be an appropriate reflection of insulin resistance [32] and also provides a (steady-state) approach similar to that obtained in the analysis with both ISI and IRI.

Group values are expressed as means and standard deviation (S.D.). Pearson's correlation coefficients were calculated to study the crude association of the glucose and (pro)insulin parameters with the various cardiovascular risk factors. All skewed data were log-transformed before these calculations were made. We use the correlations only to describe and compare the various unadjusted (inter)relationships of the parameters used in the regression analysis. The multiple *P*-values should not be interpreted nominally, but serve only as an indicator of the precision of the correlation.

By means of three multiple linear regression analyses, we compared the magnitude of the relationship between ISI, IRI and ISI + PI with TG, HDL-C, diastolic, systolic and mean blood pressure and pulse pressure, adjusted for age, sex, BMI and WHR. ISI, IRI and ISI + PI may differ according to the scales on which they are expressed, so they were transformed into *z*-scores with mean scoring 0 and S.D. scoring 1, in order to permit mutual comparison of the various regression equations.

Two multiple linear regression analyses were applied to examine the associations of two measurements of beta-cell integrity, PI versus PI:ISI, independently of WHR, BMI, age, sex and ISI. In the second analysis, adjustments were also made for glycaemic level. Different glycaemic parameters were used, because fasting glucose, but not HbA_{1c}, was correlated with blood pressure, whereas HbA_{1c}, but not glucose, remained correlated with HDL-C and TG after adjustment for WHR, BMI, age and sex.

Interaction (effect modification) between the various independent variables was finally tested

by entering product-terms into the regression equation. Residual plots were used to check the assumptions of the regression models. Subsequently, HDL-C and TG were log-transformed to correct for skewness.

For the various regression analyses described above, the regression coefficients (*b*) with standard error (S.E.) and *P*-value, change in the multiple correlation coefficient (R^2 change: change in proportion of variance explained by adding the determinant at issue to the model), or the partial correlation coefficient of the regression equations, are presented.

3. Results

Table 1 shows the population characteristics stratified according to gender. Apart from WHR and HDL-C, only small differences between the two sexes are found for the various variables.

Table 2 demonstrates moderate to highly significant positive correlation coefficients for fasting insulin, proinsulin and glucose parameters with the various cardiovascular risk factors. The PI:ISI ratio is significantly associated with most risk factors, except for DBP. HbA_{1c} is associated with most variables, but not with blood pressure.

Table 3 shows the results of the regression analysis of fasting ISI, IRI and PI + ISI as determinants of serum lipid and blood pressure parameters, adjusted for age, sex, BMI and WHR. A 1.3-fold stronger inverse association with HDL-C levels is found for IRI than for ISI ($b_{z\text{-score}} = -0.023$ and -0.018 , respectively), with a 1.6-fold better fit. IRI has a 1.6-fold stronger association with TG levels than ISI ($b_{z\text{-score}} = 0.041$ and 0.026 , respectively), with a 2.5-fold better fit. In contrast, compared to ISI, the association of IRI with blood pressure parameters is 1.5–1.9-fold weaker, with a 2.1–3.8-fold lower explained proportion of variance of the regression equation. There is a tendency towards stronger associations of PI + ISI than ISI with lipids and blood pressure.

Table 4 shows the results of multiple linear regression analysis of ISI and PI levels (Eq. (1)), and ISI and PI:ISI ratio (Eq. (2)), as determinants

Table 1
Clinical, metabolic and physiological variables, stratified for sex

	Men (<i>n</i> = 193) (mean $\pm$ S.D.)	Women (<i>n</i> = 186) (mean $\pm$ S.D.)
Age (years)	62.7 $\pm$ 7.2	64.2 $\pm$ 7.0
BMI (kg/m ²)	26.1 $\pm$ 3.1	26.5 $\pm$ 3.7
WHR	0.96 $\pm$ 0.07	0.85 $\pm$ 0.07
Serum lipids (mmol/l)		
TG	1.50 $\pm$ 0.90	1.54 $\pm$ 0.79
HDL-C	1.22 $\pm$ 0.38	1.48 $\pm$ 0.37
Blood pressure (mmHg)		
DBP	83 $\pm$ 9.4	80 $\pm$ 9.4
SBP	134 $\pm$ 18	136 $\pm$ 19
MBP	100 $\pm$ 11	99 $\pm$ 12
BP _{diff}	52 $\pm$ 13	56 $\pm$ 15
Plasma glucose (mmol/l)		
Fasting	5.7 $\pm$ 0.6	5.5 $\pm$ 0.7
Post-load	6.5 $\pm$ 2.1	6.9 $\pm$ 1.8
HbA _{1c} (%)	5.4 $\pm$ 0.5	5.1 $\pm$ 0.5
Plasma ISI (pmol/l)		
Fasting	85 $\pm$ 36	81 $\pm$ 41
Post-load	419 $\pm$ 357	481 $\pm$ 387
Plasma IRI (pmol/l)		
Fasting	115 $\pm$ 53	111 $\pm$ 59
Post-load	559 $\pm$ 456	631 $\pm$ 474
Plasma PI (pmol/l)		
Fasting	12.7 $\pm$ 11.5	9.9 $\pm$ 7.9
Post-load	65.6 $\pm$ 43.6	66.9 $\pm$ 40.0
PI + ISI		
Fasting	98 $\pm$ 43	91 $\pm$ 46
Post-load	485 $\pm$ 386	546 $\pm$ 414
PI:ISI ratio		
Fasting	0.15 $\pm$ 0.12	0.13 $\pm$ 0.11
Post-load	0.20 $\pm$ 0.17	0.16 $\pm$ 0.08

Results are expressed as mean $\pm$ S.D. BMI, body-mass index; WHR, waist-to-hip ratio; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; DBP, diastolic blood pressure; SBP, systolic blood pressure; MBP, mean blood pressure; BP_{diff}, difference between SBP and DBP; IRI, immuno-reactive insulin; ISI, immuno-specific insulin; PI, proinsulin; PI + ISI, sum of PI and ISI; PI:ISI ratio, PI divided by ISI.

of serum lipids and blood pressure parameters, adjusted for age, sex, WHR and BMI. Both the PI:ISI ratio and PI are independently associated with TG levels, but not with HDL-C. The PI:ISI ratio, but not the PI levels, was associated with SBP, MBP and pulse pressure, but was dependent on glycaemia (Eq. (3)). We also found a statistically highly significant negative association between the product-term WHR $\times$ fasting ISI (partial $r = -0.18$, $P < 0.001$). This indicates that the higher the fasting insulin levels, the lower the effect of WHR is on TG levels.

4. Discussion

This study demonstrates, for the first time, that a conventional immuno-reactive insulin assay (IRI), compared to an immuno-specific insulin assay (ISI), overestimates the association of insulin with dyslipidaemia, and underestimates the association of insulin with blood pressure. These findings are partly explained by cross-reactivity of proinsulin with the IRI assay. Although the coefficients of variation and the lower limits of sensitivity are similar for both assays, qualitative differences in insulin assessment between the two assays cannot be completely ruled out. However, this does not explain the over- and underestimation of the association of IRI with serum lipids and blood pressure, respectively. Therefore, we suggest that different statistical and pathophysiological mechanisms could be responsible for this finding.

Cross-reactivity of proinsulin with the IRI assay might explain the overestimation of the relationship between IRI and TG. Since proinsulin is positively associated with TG, independent of insulin, PI strengthens the association of IRI compared to ISI with TG. This is in line with the tendency towards a stronger association of PI + ISI than ISI alone with TG.

The considerable underestimation of the relationship between IRI and blood pressure is not easily explained by this phenomenon, because PI is not independently (negatively) associated with blood pressure. It may be explained statistically by random measurement error in the IRI assay,

Table 2

Pearson correlations between the various insulin, proinsulin, glucose, serum lipids and blood pressure variables

	ISI	IRI	PI	PI:ISI	TG	HDL-C	DBP	SBP	MBP	BP _{diff}
ISI	—	0.74 ^a	0.41 ^a	−0.14 ^b	0.29 ^a	−0.25 ^a	0.30 ^a	0.27 ^a	0.31 ^a	0.16 ^a
IRI	0.74 ^a	—	0.51 ^a	0.11 ^c	0.34 ^a	−0.28 ^a	0.25 ^a	0.20 ^a	0.24 ^a	0.10 ^c
PI	0.41 ^a	0.51 ^a	—	0.73 ^a	0.36 ^a	−0.25 ^a	0.24 ^a	0.23 ^a	0.25 ^a	0.15 ^b
PI:ISI	−0.14 ^b	0.11 ^c	0.73 ^a	—	0.21 ^a	−0.10 ^c	0.10 ^c	0.15 ^b	0.13 ^b	0.13 ^b
Fasting glucose	0.34 ^a	0.38 ^a	0.38 ^a	0.25 ^a	0.20 ^a	−0.20 ^a	0.24 ^a	0.32 ^a	0.30 ^a	0.27 ^a
HbA _{1c}	−0.04	0.11 ^c	0.15 ^b	0.16 ^b	0.22 ^a	−0.17 ^a	0.08	0.01	−0.04	0.06

See legend of Table 1 for abbreviations.

^a $P < 0.001$.^b $P < 0.01$.^c $P < 0.05$.

due to cross-reactivity with proinsulin. The random error in IRI inevitably results in an underestimation of the slope of the regression line compared with the 'true' relationship estimated by ISI, if a regression analysis is carried out for blood pressure as a function of IRI. This is analogous to the well-known statistical phenomenon of 'regression to the mean' [33]. Moreover, the enhanced random error in IRI also lowers the precision of the analyses, as indicated by the higher P -value and the lower proportion of total variance explained by regression (reduced fit). This was not confirmed by our analyses, as the sum of PI and ISI showed dissimilar (stronger) associations of PI + ISI than IRI with blood pressure. However, the comparison of ISI + PI and IRI remains difficult, because the PI assessment is quantitatively and qualitatively dissimilar to the calculated difference between ISI and IRI. Proinsulin-like molecules may still induce random measurement error in the IRI assessment. This phenomenon might explain the lack of evidence of a relationship between insulin and blood pressure in various ethnic populations [34–37], such as Pima Indians and Asians, in whom relatively high proinsulin concentrations have been found [4,38].

Both parameters of beta-cell integrity, PI:ISI ratio and PI, were associated with TG levels, but not with HDL-C, whereas the PI:ISI ratio, but not PI, was associated with SBP, MBP and pulse pressure. The potentially independent relationship of PI with blood pressure may be distorted by

multi-collinearity, due to the high correlation between PI and ISI (in our study $r = 0.41$). This does not apply to the PI:ISI ratio and ISI, which had a correlation of -0.14 . Indeed, when entered into one regression model, PI and ISI show lower partial correlations and P -values than were found for PI:ISI and ISI with the risk factors. The association of PI with blood pressure was no longer statistically significant, indicating that the statistical power could be substantially reduced by collinearity. This was not the case for PI:ISI.

Apart from the problem concerning collinearity, we suggest that the PI:ISI ratio might also be a better reflection of beta-cell impairment than PI per se. Firstly, proinsulin is secreted simultaneously with insulin from the pancreas, and enhanced PI levels might also be found in insulin-resistant states. Secondly, a higher proinsulin-to-insulin ratio seems to reflect a lower insulin release, rather than a higher proinsulin response [39,40]. A pathophysiological explanation for the association of the PI:ISI ratio with TG could be incomplete suppression of the fasting hepatic very-low-density lipoprotein (VLDL) production, due to beta-cell impairment [41]. There is no clear explanation for the relationship of the PI:ISI ratio to SBP and pulse pressure. The dependency of this relationship on glycaemia could indicate that there is a glucose-mediated effect inducing arterial stiffness, as a consequence of beta-cell impairment. Indeed, isolated systolic hypertension is frequently observed in the course of glucose intolerance [42]. There is no major prob-

Table 3

Multiple linear regression analysis of both fasting ISI, IRI and ISI+PI as determinants of serum lipids and blood pressure variables

Dependent	Equation	Determinant	$b_{z\text{-score}}$	S.E.	R^2	P-value
HDL-C	1	ISI	−0.018	0.006	1.8	0.004
	2	IRI	−0.023	0.006	2.8	0.0003
	3	ISI + PI	−0.019	0.006	1.6	0.006
TG	1	ISI	0.026	0.011	1.3	0.02
	2	IRI	0.041	0.011	3.2	0.0001
	3	ISI + PI	0.033	0.011	1.9	0.003
DBP	1	ISI	1.91	0.52	3.2	0.0002
	2	IRI	1.31	0.54	1.5	0.01
	3	ISI + PI	3.77	1.01	2.7	0.001
SBP	1	ISI	3.16	0.99	2.3	0.002
	2	IRI	1.64	1.01	0.6	0.10
	3	ISI + PI	3.77	1.01	2.7	0.001
MBP	1	ISI	2.33	0.63	3.2	0.0002
	2	IRI	1.42	0.65	1.2	0.02
	3	ISI + PI	2.52	0.64	3.6	0.0001
BP _{dif}	1	ISI	1.26	0.71	0.7	0.08
	2	IRI	0.34	0.74	0.1	0.63
	3	ISI + PI	1.49	0.71	1.1	0.04

$b_{z\text{-score}}$, Regression coefficient of z -transformed ISI, IRI and PI+ISI, calculated by separate multiple linear regression equations, adjusted for age, sex, BMI and WHR; S.E., standard error; R^2 , multiple correlation coefficient (proportion of variance explained by ISI, IRI or ISI+PI).

lem of multi-collinearity in this analysis, because the correlation between PI and PI:ISI was 0.25.

Our main findings disagree with the results of Haffner et al. [24], who report that insulin, measured either by means of conventional immuno-reactive or specific insulin assay, equally correlates with cardiovascular risk factors. With regard to proinsulinaemia, our results are in accordance with the findings of Haffner et al. [23] that fasting proinsulin is independently associated with TG levels, but not with HDL-C. However, other studies have reported a positive relationship of proinsulin with both TG and HDL-C [43]. We could not confirm that the relationship of proinsulinaemia with SBP was independent of the glycaemic level, as reported by Haffner et al. [23]. In another study, no relationship could be found between proinsulin or insulin and blood pressure [43]. Apart from differences in study population, it is possible that cross-reactivity of proinsulin in the insulin assay and multi-collinearity in the analyses could play a significant role in these inconsistencies.

We conclude that in comparison with ISI, IRI overestimates the association of insulin with lipidaemia and underestimates the relationship to blood pressure. This is partly explained by cross-reactivity of proinsulin with the IRI assay. The use of non-specific insulin assays with cross-reactivity for proinsulin-like molecules might explain the inconsistencies in the relationships between insulinaemia and various cardiovascular risk factors found in previous epidemiological studies.

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Table 4

Partial correlation between fasting ISI, ISI:PI and PI with serum lipids and blood pressure

Dependent	Regression Eq. (1) ^a		Regression Eqs. (2) ^a and (3) ^a		
	Determinant	Partial <i>r</i> (<i>P</i> -value)	Determinant	Partial <i>r</i> (<i>P</i> -value)	
				Eq. (2)	Eq. (3)
HDL-C	ISI	−0.11 (0.04)	ISI	−0.16 (0.003)	−0.15 (0.004)
	PI	−0.07 (0.19)	PI:ISI	−0.05 (0.37)	−0.03 (0.61)
			HbA _{1c}	Not entered	−0.15 (0.004)
TG	ISI	0.09 (0.10)	ISI	0.17 (0.002)	0.15 (0.004)
	PI	0.13 (0.01)	PI:ISI	0.16 (0.002)	0.13 (0.014)
			HbA _{1c}	Not entered	0.15 (0.006)
DBP	ISI	0.17 (0.001)	ISI	0.21 (0.0001)	0.17 (0.001)
	PI	0.03 (0.85)	PI:ISI	0.09 (0.54)	0.06 (0.24)
			Fasting glucose	Not entered	0.09 (0.056)
SBP	ISI	0.13 (0.01)	ISI	0.20 (0.0002)	0.13 (0.003)
	PI	0.08 (0.13)	PI:ISI	0.16 (0.003)	0.09 (0.093)
			Fasting glucose	Not entered	0.23 (<0.0001)
MBP	ISI	0.17 (0.002)	ISI	0.22 (<0.0001)	0.16 (0.003)
	PI	0.02 (0.37)	PI:ISI	0.14 (0.008)	0.08 (0.13)
			Fasting glucose	Not entered	0.18 (0.0008)
BP _{dif}	ISI	0.06 (0.25)	ISI	0.13 (0.015)	0.05 (0.39)
	PI	0.10 (0.05)	PI:ISI	0.15 (0.005)	0.08 (0.14)
			Fasting glucose	Not entered	0.25 (<0.0001)

^a Adjusted for age, sex, BMI and WHR. Partial *r*, partial correlation coefficient.

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