Determinants of Specific Serum Insulin Concentrations in a General Caucasian Population aged 50 to 74 years (the Hoorn Study)

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The aim of this study was to investigate anthropometric and life-style determinants of insulinaemia. Specific fasting serum insulin (FI) was analysed in a general Caucasian population aged 50–74 years, not known to have diabetes mellitus (n = 2226, sample 1). The analysis was repeated some weeks later in a subgroup of sample 1 in which two individual measurements of FI were available (n = 540, sub-sample 2). Specific serum insulin 2 h after ingestion of 75 g glucose (2hI), also measured on two occasions, was analysed in this same subgroup after excluding 59 subjects with fasting plasma glucose >7 mmol l^{-1} (n = 481, sub-sample 3). Multiple regression analyses were performed, stratified for sex, with ^{10}log insulin as the dependent variable. All determinants were adjusted for each other. FI was positively associated with BMI and waist–hip ratio (men and women) and inversely associated with intake of fibre (women), moderate alcohol use (men), and current smoking (women). 2hI was positively associated with BMI and waist–hip ratio (men and women), and intake of fat (women). 2hI was inversely associated with physical activity and moderate alcohol use (men and women), and current smoking (men). Family history of diabetes was not associated with insulinaemia. In conclusion, various life-style factors are related to insulinaemia, independent of obesity. © **1998 John Wiley & Sons, Ltd.**

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KEY WORDS **hyperinsulinaemia; family history of diabetes; obesity; physical activity; nutrition; alcohol; smoking; life-style factors; insulin resistance**

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Introduction

Hyperinsulinaemia, reflecting insulin resistance,[1] has been shown to be predictive for the development of non-insulin-dependent (Type 2) diabetes mellitus (NIDDM) in subjects with normal glucose tolerance, and is a putative risk factor for atherosclerotic cardiovascular disease.[2,3] A well-known determinant of hyperinsulinaemia is obesity, both general and, more particularly abdominal obesity. Less clear is the role of other factors, often clustering with obesity. Some of these may contribute to hyperinsulinaemia via obesity, as for example nutritional habits, whereas others may affect insulin levels directly. One reason for inconsistency in reported relationships may be the various methods used to measure insulin concentrations. In most studies insulin concentrations were measured as a sum of insulin, proinsulin, and split-proinsulin. These data are difficult to interpret as proinsulin and split-proinsulin do not have the same biological activity as insulin and are found in relatively high concentrations in subjects with impaired or diabetic glucose tolerance.[4,5] More recent methods measure insulin specifically.

The Hoorn Study, a population-based study in which insulin concentrations were measured repeatedly with a specific assay and many potential determinants of insulin concentration were assessed, can provide more insight into the potential causes of an elevated serum insulin level. Therefore, the aim of this analysis was to examine the independent association of obesity and other factors with specific serum insulin concentrations in a white Caucasian population aged 50–74 years.

Patients and Methods

Study Population

This analysis is based on cross-sectional data from the Hoorn Study, collected between 1989 and 1992 in the Dutch city of Hoorn (56 000 inhabitants). The Hoorn Study is a population-based survey of glucose tolerance and cardiovascular diseases among white Caucasians. Caucasian ethnicity was defined as having at least 3 grandparents from European or Mediterranean countries

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(self-reported data). The sampling procedures are described in Figure 1. Fasting insulin levels were analysed in two samples: sample 1 (n = 2226) was representative of the Caucasian inhabitants of Hoorn, aged 50–74 years, without a history of diabetes. In this sample, fasting insulin was measured once. In sub-sample 2 (n = 540), a subgroup of sample 1 stratified for age, sex, and glucose tolerance, repeated measurements of fasting insulin for each individual (interval 2–6 weeks) were available.

Two-hour post 75 g oral glucose load insulin levels, also measured twice, were analysed in sub-sample 3 (n = 481). This group comprised sub-sample 2, after the exclusion of subjects with fasting glucose levels greater than 7 mmol l^{-1} (n = 59). This selection was done in order to exclude subjects with a substantial beta-cell dysfunction. The study design has previously been described in more detail.[6]

Determinants of Hyperinsulinaemia

Family history of diabetes was defined as 'positive' if any of the subject's grandparents, parents, brothers, sisters or children had a history of diabetes (self-reported data). Height and weight were measured without shoes and outer garments, and BMI was calculated as weight (in kg) divided by the square of the height (in m^2). Waist and hip measurements were taken, according to a standardized procedure.[7] Waist–hip ratio (WHR) was defined as waist circumference divided by hip circumference. Physical activity was measured by a questionnaire, originally designed for use in elderly Dutch men.[8] As the participants in our survey were younger and also included women, we adapted this questionnaire slightly, resulting in nine questions (yes/no) about the regular performance of the following: sport, bicycling, gardening, walking, doing odd jobs, climbing the staircase at home, household activities, daily food shopping and employment (paid or unpaid). The questions were equally weighted, so the range of the physical activity score was 0 to 9. Dietary habits, including alcohol intake, were measured by a semi-quantitative food frequency questionnaire, filled in by the subjects at home and checked in a personal interview with the participant at the research centre. This questionnaire contained 92 questions about an extensive variety of foodstuffs and proved to have a good relative validity as assessed by comparing questionnaire data with interview data collected by a dietician during a home visit.[9] Current smoking was assessed by asking 'do you smoke now'? (yes/no).

Laboratory Analysis

The laboratory analyses, including the determination of the coefficients of analytical variation (CV_a), were performed at the University Hospital of the Vrije Universiteit Amsterdam. Glucose was measured with a glucose dehydrogenase method (Merck, Darmstadt, Germany). Immunospecific insulin was measured in serum by a double-antibody radioimmunoassay (lot SP21, Linco Research, St. Louis, USA), 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.[10] The inter-assay CV_a, was 6% at insulin levels in the range of 40–1000 p mol l^{-1}. The lower limit of sensitivity was 12 p mol l^{-1}.

Statistical Analysis

Determinants of fasting and 2-h insulin levels were studied by means of multiple regression analyses, combining all determinants into one model. As the determinant 'nutrition' consisted of 13 variables (see Table 1), a pre-analysis (multiple regression) was done with a single nutrition variable as the independent and fasting or 2-h insulin levels as the dependent variable. Only those single nutrition variables were added to the final regression analysis of insulin levels (as shown in Figures 2, 3, and 4), which had a 'crude' (adjusted for energy intake only) and an 'adjusted' significant (defined as $p < 0.10$) association with insulin levels in men or in women. 'Adjusted' meant corrected for energy intake, BMI, and WHR. Alcohol use was analysed by constructing two dichotomous dummy variables: [no alcohol] = 0 versus [use of >0 g day^{-1}] = 1, and [use of ≤ 30 g day^{-1}] = 0 versus [use of >30 g day^{-1}] = 1. Because both variables were entered simultaneously into the regression analyses, the first variable assesses the association of moderate alcohol (>0 and ≤ 30 g day^{-1}) versus no alcohol use with insulin levels, while the second variable gives information on 'heavy' alcohol (>30 g day^{-1}) versus moderate alcohol use. Fasting and 2-h insulin values were ^{10}log-transformed to correspond with the assumptions of regression analysis and the resulting regression coefficients have been re-transformed to percentage differences in insulin values, associated with a specified difference in the determinant variable. For example, the regression coefficient of the adjusted association of BMI in women (SE: 3.885 kg m^{-2}, see Table 1) with once-measured ^{10}log fasting insulin (pmol l^{-1}) was 0.012916. Consequently, a difference of +2SD in BMI in women is associated with a difference by a factor of $10^{2*3.885*0.012916} = 10^{0.1003573} = 1.26$, or a difference of +26 % in once-measured fasting insulin levels. Test results were considered to be statistically significant if two-sided p-values were less than 0.05. The nutritional analyses yielded similar results, irrespective of whether we expressed nutrition in terms of absolute quantities or in energy percentages. Therefore, we present here the results in terms of energy percentage only.

Results

Table 1 shows the characteristics of sample 1. Due to our sampling procedures, subjects in sub-sample 2 are

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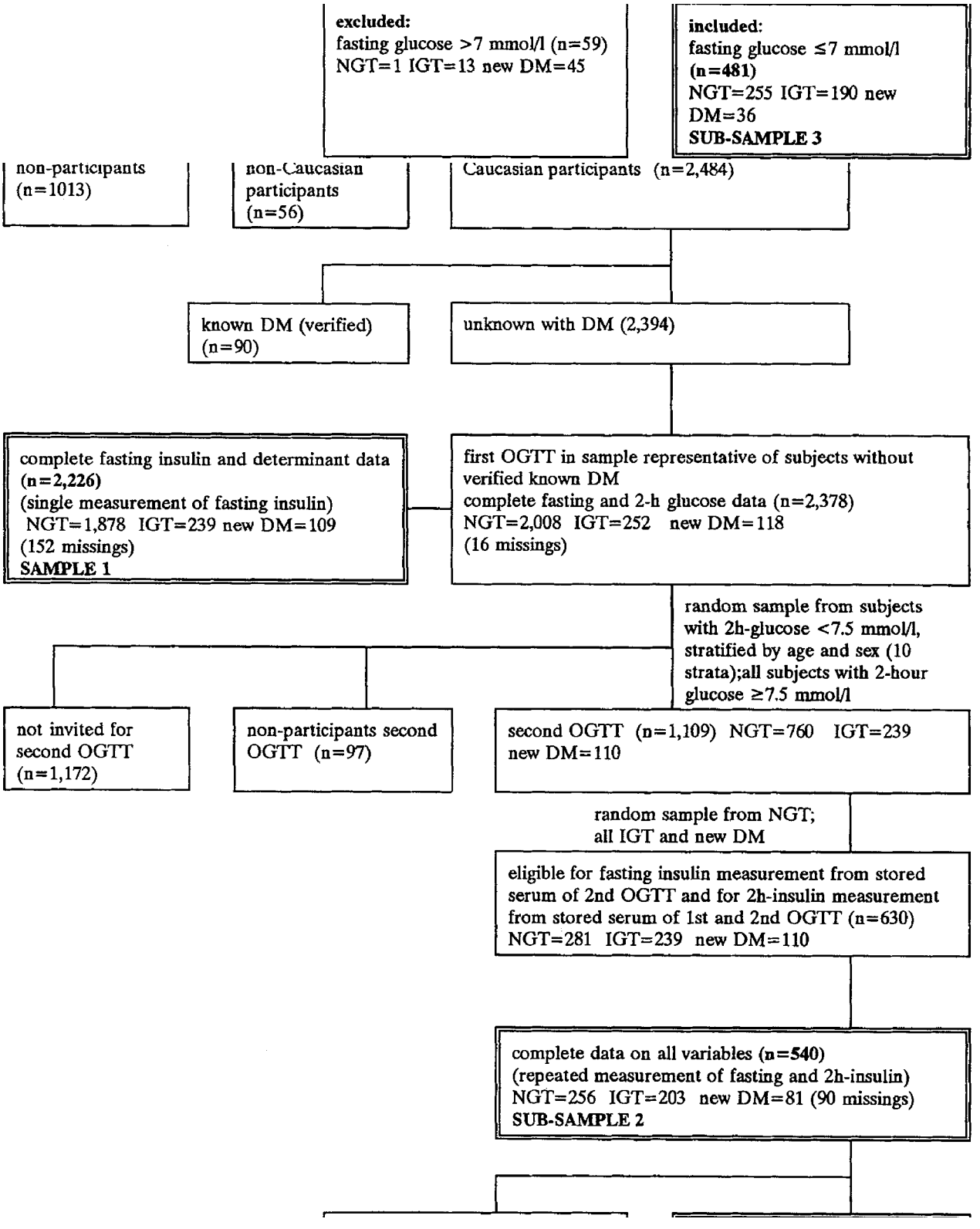

Figure 1. Sampling procedure for the present analyses: NGT, IGT, and new DM indicate normal, impaired glucose tolerance and newly detected diabetes mellitus, respectively, as classified at first OGTT

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Table 1. Subject characteristics in sample 1 (see Figure 1)

	Men (n = 1013)			Women (n = 1213)			All (n = 2226)		
	NGT 863	IGT 99	New DM 51	NGT 1015	IGT 140	New DM 58	NGT 1878	IGT 239	New DM 109
Age (years)	61 ± 7			62 ± 7			61 ± 7		
Fasting serum insulin (pmol l^{-1})	78 (58, 107)			76 (55, 107)			77 (57, 107)		
Fasting plasma glucose (mmol l^{-1})	5.5 (5.1, 6.0)			5.3 (4.9, 5.9)			5.4 (5.0, 6.0)		
2-h plasma glucose (mmol l^{-1})	5.3 (4.1, 7.1)			5.6 (4.4, 7.3)			5.5 (4.2, 7.2)		
Body mass index (kg m^{-2})	26 ± 3			27 ± 4			26 ± 3		
Waist–hip ratio	0.95 ± 0.06			0.84 ± 0.07			0.89 ± 0.09		
Family history of DM (% yes)	25			28			26		
Physical activities (range 0–9), n	5.7 ± 1.6			5.6 ± 1.5			5.6 ± 1.6		
Alcohol use (% distribution)[a]	17;71;12			42;54;4			30;62;8		
Curent smoking (% yes)	36			28			31		
Daily nutrient intake									
energy (kcal × 1000)	2.3 ± 0.6			1.9 ± 0.5			2.1 ± 0.6		
protein total (E%)	14.2 ± 2			15 ± 3			15 ± 3		
vegetable	4 ± 1			4 ± 1			4 ± 1		
animal	10 ± 3			11 ± 3			10 ± 3		
fat total (E%)	41 ± 6			41 ± 6			41 ± 6		
saturated	17 ± 3			17 ± 3			17 ± 3		
monounsaturated	15 ± 3			15 ± 3			15 ± 3		
polyunsaturated	8 ± 3			8 ± 3			8 ± 3		
carbohydrate total (E%)	41 ± 6			42 ± 7			42 ± 6		
mono- and disaccharides	20 ± 6			21 ± 6			20 ± 6		
polysaccharides	21 ± 4			21 ± 4			21 ± 4		
alcohol (E%)	4 ± 5			2 ± 3			3 ± 4		
dietary cholesterol (g)	0.3 ± 0.1			0.3 ± 0.1			0.3 ± 0.1		
dietary fibre (g)	28 ± 9			26 ± 7			27 ± 8		

Results as means ±SD or median (20th, 80th percentile) or percentage.
NGT, normal glucose tolerance; IGT, impaired glucose tolerance; new DM, newly detected diabetes mellitus; E%, energy percentage.
[a]% distribution over 3 categories: 1. none, 2. >0 and ≤30 g day^{-1}, and 3. >30 g day^{-1}.

slightly older and have higher glucose and insulin levels, compared to sample 1. (Sub-sample 2: mean (SD) age: 64 ± 7 years. Median (20th, 80th percentile) of fasting glucose and fasting insulin: 5.7 (5.2, 6.5) mmol l^{-1} and 83 (59, 125) pmol l^{-1}, respectively). Sub-sample 3 consists of sub-sample 2, with the exclusion of persons with fasting hyperglycaemia. Therefore, median glucose and insulin values in sub-sample 3 are slightly lower as compared to those in sub-sample 2. (Sub-sample 3: median (20th, 80th percentile) fasting glucose and fasting insulin: 5.6 (5.1, 6.2) mmol l^{-1} and 81 (57, 117) pmol l^{-1}, respectively).

Determinants of Fasting and 2-h Insulin Levels

Figure 2 gives a graphical representation of the results of the multiple regression analysis in the representative sample 1 with once-measured ^{10}log fasting insulin as dependent variable and potential determinants (as shown on the x-axis) as independent variables, all adjusted for each other.

Figure 3 shows similar results for the stratified sub-sample 2 where ^{10}log fasting insulin levels were computed as the individual average of two measurements. From the pre-analysis of 13 nutrition variables only fibre intake in women appeared to be significantly associated with ^{10}log fasting insulin (once-measured as well as twice-measured), so this variable was added to the final fasting insulin regression model. Figure 4 shows similar results for the stratified sub-sample 3 with ^{10}log 2-h insulin as dependent variable, again computed as the individual average of two measurements. The pre-analysis of 13 nutrition variables showed that only total fat intake in women was related to ^{10}log 2-h insulin levels and therefore we added this variable to the final 2-h insulin regression model.

Figures 2, 3, and 4 can be read as follows: if the vertical bar of the confidence interval does not cross the horizontal zero line, the association is statistically significant with a p-value of at least <0.05. The greater the distance of the point estimate to the horizontal zero line, and the narrower the confidence interval, the smaller the p-value. Considering these three figures, determinants of hyperinsulinaemia can be divided in five groups:

1. Those having a strong association with fasting and 2-h insulin in all analyses, i.e. BMI and WHR.
2. Those having no relationship with insulin levels in all analyses, i.e. family history of diabetes.

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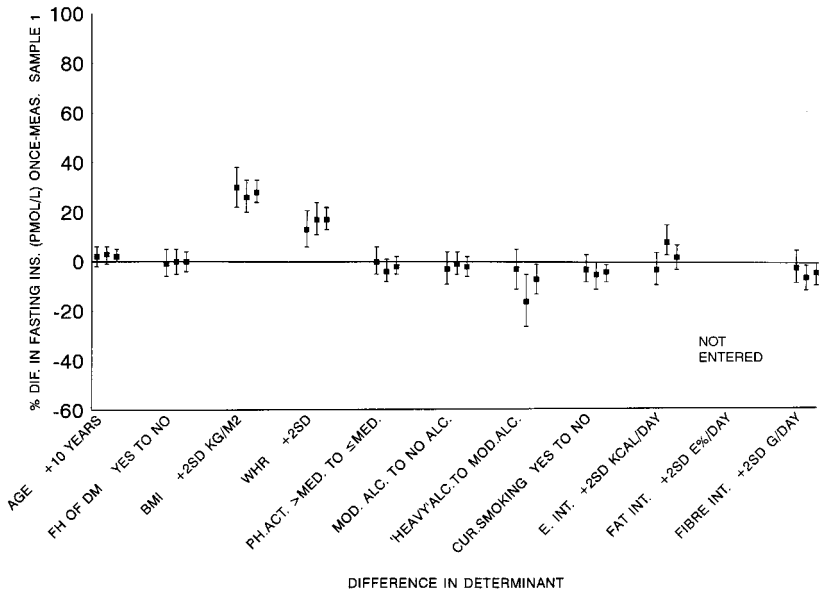

Figure 2. Sample 1: results of a multiple regression analysis with ^{10}log fasting insulin (once-measured) as dependent variable and potential determinants, adjusted for each other, as independent variables. First bar: men (n = 1013); second bar: women (n = 1213); third bar: all (n = 2,226). DIF., difference; MEAS., measured; FH of DM, family history of diabetes; BMI, body mass index, WHR, waist–hip ratio; PH.ACT., physical activity; MED, median; MOD:ALC, moderate alcohol use; CUR., current; E.INT., energy intake

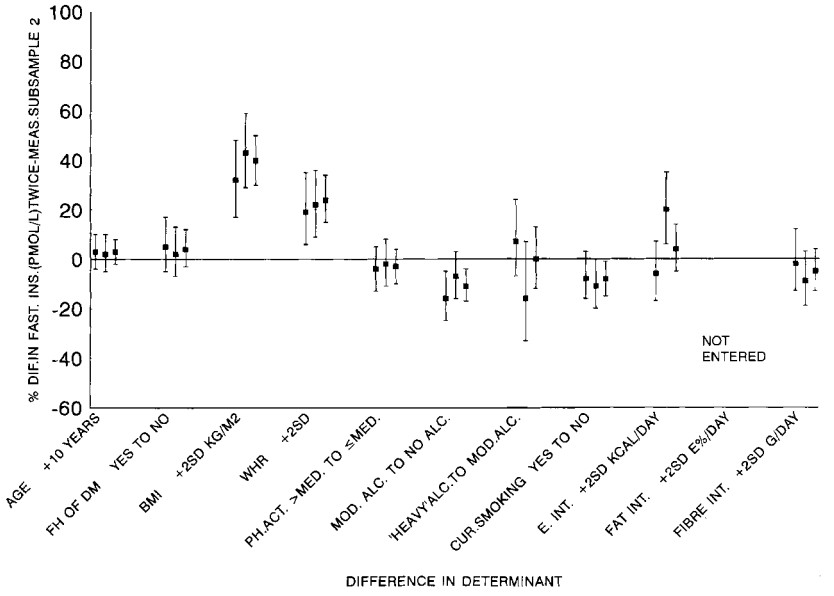

Figure 3. Sub-sample 2: results of a multiple regression analysis with ^{10}log fasting insulin (twice measured) as dependent variable and potential determinants, adjusted for each other, as independent variables. First bar: men (n = 263); second bar: women (n = 277); third bar: all (n = 540). FAST.INS., fasting insulin. For other abbreviations, see Figure 2

3. Those having weak associations in some of the analyses with fasting and with 2-h insulin (moderate alcohol and current smoking).
4. Those having weak associations in some of the analyses with fasting insulin only (fibre intake) or with 2-h insulin only (age, physical activity, and fat intake).
5. Those having an inconsistent association (different directions) with insulin levels, i.e. energy intake.

When pooling data of both sexes, the explained variance of once-measured fasting insulin levels in the large representative sample 1 was 17%. The explained variance of twice-measured fasting insulin (in sub-sample 2) was 30% and of twice-measured 2-h insulin (in sub-sample 3) 28%.

To answer the question whether a second measurement of insulin levels has an additional value, data from the same sample have to be compared. Therefore, we repeated the analysis in the stratified sub-sample 2 (n = 540) with once-measured fasting insulin instead of twice-measured insulin as dependent variable (data not shown). The results were rather similar; the explained variance of once-measured fasting insulin was 28 % (versus 30 %

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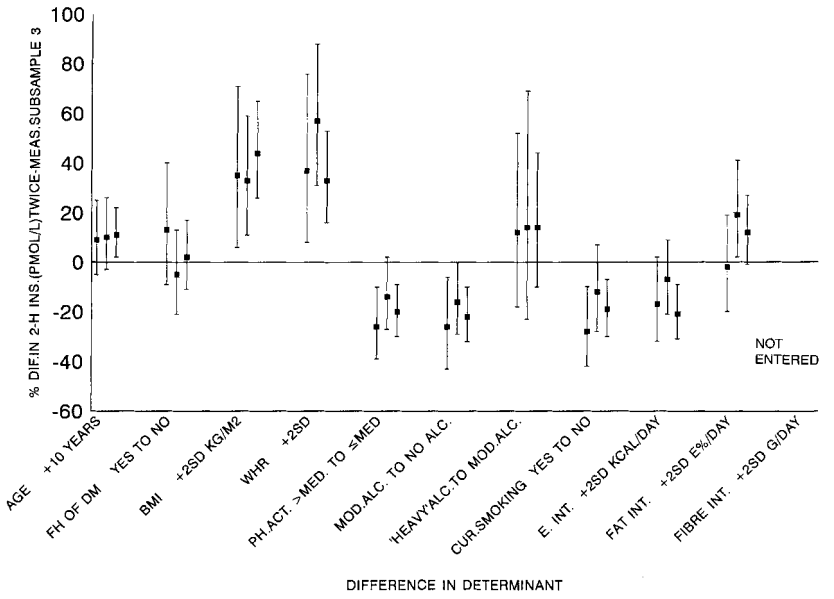

Figure 4. Sub-sample 3: results of a multiple regression analysis with ^{10}log 2-h insulin (twice measured) as dependent variable and potential determinants, adjusted for each other, as independent variables. First bar: men (n = 231); second bar: women (n = 250); third bar: all (n = 481). 2-H INS., 2-h insulin. For other abbreviations, see Figure 2

of twice-measured fasting insulin). The same determinants turned out to be significant in the model, irrespective if insulin levels were based on one or two measurements. With respect to 2-h insulin, we repeated the analysis in the stratified sub-sample 3 (n = 481) with once-measured, instead of twice-measured 2-h insulin as dependent variable. Again, similar results were found (data not shown): the same determinants reached significance, except for total fat intake in women, which was borderline significant (p = 0.09). The explained variance of once-measured 2-h insulin was 24% (versus 28 % of twice-measured 2-h insulin).

Discussion

Fasting insulin concentrations are used in epidemiological studies as a measure of insulin sensitivity. Insulin levels 2 h after a 75 g glucose load reflect insulin sensitivity also, except in subjects with NIDDM, with substantial defects in both insulin secretion and insulin action.[1] Laakso found that 50 % of insulin action in peripheral tissues (as measured by the euglycaemic hyperinsulinaemic clamp technique) at most can be explained by an once-measured individual plasma insulin level.[1] In the present study, our regression models only explained up to 30 % of the variance in insulin levels. Consequently, interpretation of our results in terms of insulin sensitivity has to be done with caution.

Measurement of life-style determinants as nutrition and physical activity by questionnaire is imprecise, the effect of which will be to reduce its association with hyperinsulinaemia towards the null value. Therefore the quantitative estimates of the association between these life-style factors and hyperinsulinaemia found in the present study and discussed below, probably will be an underestimation.

In most of our models, age was not associated with hyperinsulinaemia. This strengthens the hypothesis that insulin resistance is more related to obesity than to age,[11] and supports the recent findings of a multinational European study, in which no association was found between insulin sensitivity (measured with the euglycaemic clamp) and age.[12]

Self-reported family history of diabetes was not associated with hyperinsulinaemia. Although it might be argued that self-reported family history of diabetes is an invalid estimate of family risk for diabetes, a previous analysis of Hoorn Study data found a positive family history of diabetes to be associated with higher 2-h glucose levels, suggesting that it measures to some extent a family disposition towards diabetes.[13] Other European studies have also failed to find hyperinsulinaemia among relatives of NIDDM patients.[14,15] However, ethnic differences may exist, as in a Mexican-American population higher specific insulin levels were found to be associated with a parental history of diabetes.[16]

Even with our crude measurement of physical activity, we found that more active persons had lower insulin levels 2 h after a glucose load. The association between physical activity and hyperinsulinaemia has been reported by others.[17–20] It should be noted that in our study physical activity was defined mainly in terms of daily activities which require no vigorous exercise.

Moderate alcohol use was weakly associated with lower insulin levels. Therefore, our population-based data are consistent with experimental findings that light-to-moderate alcohol intake is associated with enhanced insulin sensitivity, and is compatible with suggestions

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that moderate alcohol use not only lowers the risk of cardiovascular disease, but also of diabetes mellitus.[21] The significant inverse association of 'heavy' alcohol use with fasting insulin in women is difficult to interpret as only 4 % of the women were 'heavy' drinkers.

Remarkably, we found an inverse association of smoking with insulin levels, even after adjusting for obesity. Experimental studies have reported an opposite association.[22,23] Selective cardiovascular mortality in those who have both risk factors, i.e. smoking and hyperinsulinaemia, might partly explain our cross-sectional finding.

A low fibre intake and a high fat intake were associated with hyperinsulinaemia in women only. For all associations of fibre and fat intake with insulin levels, the point estimates for women fell within the confidence interval of the point estimate for men (see Figures 2, 3, and 4), implying that the difference between men and women was not statistically significant. Other studies have reported that high-fat (especially saturated fat) and low-fibre intake are associated with hyperinsulinaemia, although it is not always clear how far these associations are mediated by obesity.[24–27] Our data did not show significant associations of specific forms of fat with 2-h post-glucose load insulin levels, due to the fact that the precision of these data was too low.

If the intra-individual biological and/or analytical variation contributes substantially to the total variance of insulin levels, we might expect that the analysis based on twice-measured insulin would yield a substantial gain in precision, compared to the analysis based on once-measured insulin. As this was not the case, it is suggested that the variance of fasting and 2-h post-glucose load insulin is mostly determined by the inter-individual variation, which will be unaffected by repeated measurements. The lower percentage explained variance found in the large representative sample 7 is probably due to the latters different composition compared to subsamples 2 and 3.

In summary, we find that self-reported family history of diabetes in middle-aged white Caucasians is not related to hyperinsulinaemia. High-fibre, low-fat nutrition, moderate alcohol use, moderate physical activity and, unexpectedly, smoking may be associated with lower insulin levels, independent of obesity. In epidemiological analyses, the additional value of a second insulin measurement, taken some weeks later, is relatively small.

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