

# Insulin Resistance, Impaired Early Insulin Response, and Insulin Propeptides as Predictors of the Development of Type 2 Diabetes

A population-based, 7-year follow-up study in 70-year-old men

BJÖRN ZETHELIUS, MD<sup>1</sup>  
C. NICHOLAS HALES, PHD<sup>2</sup>

HANS O. LITHELL, MD<sup>1</sup>  
CHRISTIAN BERNE, MD<sup>3</sup>

**OBJECTIVE** — Defects in insulin secretion and insulin action are the major abnormalities in the development of type 2 diabetes. In middle-aged subjects, elevated plasma proinsulin has been found to predict type 2 diabetes. Therefore, our aim was to study the longitudinal relationships between baseline determinations of insulin sensitivity index ( $S_i$ ) assessed by euglycemic insulin clamp, the early insulin response (EIR) at an oral glucose tolerance test (OGTT), fasting intact proinsulin, 32–33 split proinsulin and specific insulin, and the development of type 2 diabetes in a population-based cohort of 70-year-old nondiabetic men ( $n = 667$ ) with 7-year follow-up.

**RESEARCH DESIGN AND METHODS** — A euglycemic insulin clamp study and a 75-g OGTT were performed at baseline, and fasting peptide concentrations were measured using specific two-site immunometric assays. Results from logistic regression models are presented as odds ratios (ORs) with 95% CIs for a 1-SD increase in the predictor variable.

**RESULTS** — In separate multivariate analyses adjusted for EIR (OR 0.72, 95% CI 0.59–0.89) and  $S_i$  (0.68, 0.58–0.88), 32–33 split proinsulin (1.49, 1.18–1.88) or intact proinsulin (1.30, 1.04–1.63) were significantly associated with the development of type 2 diabetes, whereas specific insulin (1.24, 0.91–1.66) was not. The significant associations between 32–33 split or intact proinsulin and the development of type 2 diabetes were unaltered after adjustment for BMI and glucose tolerance.

**CONCLUSIONS** — Insulin propeptides predicted type 2 diabetes over a 7-year period in elderly men, independent of the EIR and  $S_i$ .

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Impaired insulin secretion and impaired insulin action are the major defects underlying the development of type 2 diabetes (1,2). A low early insulin response (EIR) to a glucose load (2–6), fasting hyperinsulinemia (4,7,8), and in-

ulin resistance assessed with clamp technique (6) have been shown to predict type 2 diabetes in prospective studies. Furthermore, fasting concentrations of proinsulin-like molecules (PLMs), i.e., the sum of intact and 32–33 split proinsulin, pre-

dicted the onset of type 2 diabetes in middle-aged subjects with a follow-up of up to 4 years (9–12). In three studies, including a long-term follow-up study (13) in which specific methods for intact and 32–33 split proinsulin measurements were used, both intact and 32–33 split proinsulin were independent predictors of type 2 diabetes (13–15).

Both proinsulin and specific insulin are correlated to measurements of insulin resistance and EIR in normoglycemic subjects (16). The simultaneous assessment of 32–33 split proinsulin and intact proinsulin, EIR, and insulin resistance measured with the euglycemic insulin clamp technique to characterize the strength of these predictors of type 2 diabetes has not been performed in an elderly population. Therefore, the aim of this study was to investigate whether intact proinsulin, 32–33 split proinsulin, specific insulin, and immunoreactive insulin (IRI) predicted the development of type 2 diabetes in 70-year-old nondiabetic men at baseline, when determinations of EIR at an oral glucose tolerance test (OGTT) and insulin sensitivity ( $S_i$ ) by the euglycemic insulin clamp (17) were taken into account, and if further adjustment for BMI or glucose tolerance at an OGTT would alter such a possible significant predictor by outcome associations.

## RESEARCH DESIGN AND METHODS

In 1970, all men (predominantly Caucasians) born between 1920 and 1924 and residing in Uppsala were invited to a health survey in which 82% ( $n = 2,322$ ) participated (18). After 20 years, at 70 years of age, they were invited for reinvestigation performed from August 1991 to May 1995, which formed the baseline of the present study comprising 1,221 men of 1,681 who were still living (73%) (19).

A 75-g OGTT was performed at base-

From the <sup>1</sup>Department of Public Health and Caring Sciences, Section of Geriatrics, Uppsala University, Uppsala, Sweden; the <sup>2</sup>Department of Clinical Biochemistry, Addenbrooke's Hospital, Cambridge, U.K.; and the <sup>3</sup>Department of Medical Sciences, Uppsala University, Uppsala, Sweden.

Address correspondence and reprint requests to Björn Zethelius, MD, Department of Public Health and Caring Sciences, Section of Geriatrics, Uppsala University, Box 609, SE-75125 Uppsala, Sweden. E-mail: bjorn.zethelius@pubcare.uu.se.

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**Abbreviations:** EIR, early insulin response; IGT, impaired glucose tolerance; IRI, immunoreactive insulin; OGTT, oral glucose tolerance test; P:I, proinsulin to specific insulin; PLM, proinsulin-like molecule; WHR, waist-to-hip ratio.

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**Table 1—Characteristics at baseline for the study population and univariate ORs, for the development of type 2 diabetes over the 7-year follow-up**

	Baseline	OR (95% CI)	P	Nonconverters	Converters	P
S <sub>i</sub> (mg · min <sup>-1</sup> · kg <sup>-1</sup> [100 mU/l])	5.4 ± 2.4	0.64 (0.52–0.78)	0.001	5.7 ± 2.4	4.9 ± 2.6	0.005
EIR (pmol/mmol)	28.6 ± 20.5	0.89 (0.74–1.07)	0.225	28.0 ± 20.7	26.7 ± 19.8	0.39
Proinsulin (pmol/l)	7.0 ± 5.2	1.39 (1.16–1.68)	0.001	6.3 ± 4.0	8.1 ± 6.4	0.001
32–33 split proinsulin (pmol/l)	9.3 ± 9.2	1.55 (1.28–1.88)	0.001	8.0 ± 6.4	11.3 ± 9.8	0.001
Specific insulin (pmol/l)	47.9 ± 29.5	1.34 (1.12–1.63)	0.002	46.6 ± 35.5	55.6 ± 38.7	0.01
Proinsulin-to-insulin ratio	0.16 ± 0.11	1.04 (0.86–1.26)	0.671	0.15 ± 0.1	0.16 ± 0.1	0.77
Immunoreactive insulin (pmol/l)	73.2 ± 41.1	1.24 (1.03–1.50)	0.021	70.8 ± 38.9	77.4 ± 48.4	0.07
Fasting plasma glucose (mmol/l)	5.3 ± 0.6	2.61 (2.11–3.24)	0.001	5.2 ± 0.5	5.7 ± 0.7	0.001
2-h plasma glucose (mmol/l)	6.9 ± 1.8	2.02 (1.66–2.45)	0.001	6.7 ± 1.8	7.9 ± 1.9	0.001
IGT vs. NGT (%)	30.1	3.11 (2.14–4.54)	0.001	25.1	51	0.001
BMI (kg/m <sup>2</sup> )	26.0 ± 3.2	1.32 (1.10–1.59)	0.002	25.9 ± 3.1	26.7 ± 3.2	0.01
WHR	0.94 ± 0.05	1.24 (1.04–1.49)	0.017	0.93 ± 0.05	0.94 ± 0.06	0.16

Data are arithmetic means ± SD and OR (95% CI); *n* = 47/667. Logistic regression was applied to variables standardized to 1 SD. Means ± SD and *P* values for Student's *t* tests between nonconverters and converters to type 2 diabetes are also shown. EIR = early insulin response at an OGTT ( $\Delta 0$ –30 insulin/ $\Delta 0$ –30 glucose). All analyses were adjusted for age at baseline.

line. Diabetes and impaired glucose tolerance (IGT) were defined according to the 1999 World Health Organization (WHO) criteria (20). Subjects who were diagnosed with diabetes at the OGTT or used any pharmacologic treatment for diabetes were excluded from the baseline population of this study. Accordingly, 196 men with diabetes, 2 men without OGTT data, and 13 men without propeptide data were excluded, leaving 1,010 nondiabetic men in the baseline population. The study was approved by the Ethics Committee of the Faculty of Medicine at Uppsala University. Written informed consent was obtained from all subjects.

### Follow-up and outcome

All living men (*n* = 1,079 of 1,221) were invited to a follow-up investigation at 77 years of age. Subjects were investigated between October 1997 and June 2001, with a follow-up of 7 years from baseline. In total, 840 (78%) men were investigated with a medical questionnaire, according to the original protocol (18,21), and their fasting plasma glucose concentrations were determined. Type 2 diabetes, at follow-up, was defined as a fasting plasma glucose  $\geq 7.0$  mmol/l (20) or use of oral hypoglycemic agents, which also covered all those that had answered that they have type 2 diabetes in the questionnaire. The present study was based on nondiabetic subjects at baseline who attended the follow-up at 77 years of age (*n* = 667).

To avoid potential bias by using only fasting glucose concentrations for the diagnosis of type 2 diabetes at follow-up

when defining nondiabetic subjects using data from a 75-g OGTT at baseline, an additional analysis was performed defining type 2 diabetes at baseline as a fasting plasma glucose level  $\geq 7.0$  mmol/l (20) or the use of oral hypoglycemic agents.

### Euglycemic insulin clamp

S<sub>i</sub> was determined with the euglycemic insulin clamp technique (17), with insulin infused at a constant rate of 56 mU/(min · m<sup>2</sup>), calculated to achieve nearly complete suppression of hepatic glucose output. S<sub>i</sub> was calculated as glucose disposal rate (mg glucose infused/min · kg body wt) divided by the mean plasma insulin concentration times 100 (mU/l) during the last 60 min of the 2-h clamp.

### OGTT

Glucose tolerance was assessed by a 75-g OGTT, separated in time by 1 week from the clamp procedure (20). Concentrations of plasma glucose were analyzed by the glucose dehydrogenase method (Gluc-DH; Merck, Darmstadt, Germany). EIR was defined as the ratio of the 30-min increment in insulin concentration to the 30-min increment in glucose concentration after oral glucose loading (22).

### Proinsulin and insulin determinations

Blood samples for fasting concentrations were collected after an overnight fast. The concentrations of intact proinsulin and 32–33 split proinsulin were analyzed using the two-site immunometric assay technique (23) in plasma samples that

had been stored frozen ( $-70^{\circ}\text{C}$ ) since baseline. Specific insulin concentrations were also determined in these samples using the Access Immunoassay System (Sanofi Pasteur Diagnostics, Marnes-la-Coquette, France). Analyses were performed, blinded for outcome, at the Department of Clinical Biochemistry, Addenbrooke's Hospital (Cambridge, U.K.). Serum IRI concentrations were determined, at baseline, with the enzymatic immunologic assay Enzymmmun (Boehringer Mannheim, Mannheim, Germany) (19). A comparison between IRI and the sum of specific insulin and the PLMs, using a Bland-Altman plot (24), did not disclose any nonlinear relationships or any trend for the mean difference to rise or fall with increasing concentrations (*r* =  $-0.038$ , *P* = 0.28).

### Anthropometric measurements

Weight, height, BMI (kg/m<sup>2</sup>), and waist-to-hip ratio (WHR) were measured under standardized conditions according to the baseline protocol (25).

### Statistical analyses

Skewed variables (insulin, PLMs, and fasting blood glucose) were log transformed to achieve normal distribution. Normally distributed variables were used in all statistical analyses, performed using the statistical software package STATA 6.0 for PC (STATA, College Station, TX). All tests were two tailed, and a *P* value  $< 0.05$  was considered significant. Logistic regression analyses were used on standardized variables (standardized to 1 SD)

**Table 2—Multivariate ORs for the development of type 2 diabetes over the 7-year follow-up, including  $S_i$  and EIR, and with 32–33 split proinsulin or with intact proinsulin added, without or with adjustment for BMI and glucose tolerance**

	OR (95% CI)	P
Model 1		
EIR (1 SD)	0.73 (0.60–0.90)	0.003
$S_i$ (1 SD)	0.55 (0.43–0.70)	0.001
Model 2		
32–33 split proinsulin	1.52 (1.18–1.95)	0.001
Specific insulin	1.03 (0.81–1.32)	0.786
Model 3		
Proinsulin	1.27 (1.03–1.61)	0.036
Specific insulin	1.15 (0.91–1.47)	0.230
Model 4		
32–33 split proinsulin (1 SD)	1.49 (1.18–1.88)	0.001
EIR (1 SD)	0.71 (0.58–0.87)	0.001
$S_i$ (1 SD)	0.68 (0.53–0.88)	0.004
Model 5		
Proinsulin (1 SD)	1.30 (1.04–1.63)	0.023
EIR (1 SD)	0.72 (0.59–0.89)	0.002
$S_i$ (1 SD)	0.65 (0.50–0.83)	0.001
Model 6		
32–33 split proinsulin (1 SD)	1.39 (1.08–1.76)	0.009
EIR (1 SD)	0.77 (0.62–0.95)	0.015
$S_i$ (1 SD)	0.79 (0.59–1.05)	0.109
BMI (1 SD)	1.05 (0.83–1.34)	0.677
IGT vs. NGT	2.09 (1.36–3.20)	0.01
Model 7		
Proinsulin (1 SD)	1.28 (1.02–1.61)	0.034
EIR (1 SD)	0.78 (0.63–0.97)	0.025
$S_i$ (1 SD)	0.77 (0.57–1.03)	0.074
BMI (1 SD)	1.09 (0.86–1.39)	0.448
IGT vs. NGT	2.18 (1.43–3.34)	0.001

Logistic regression was applied to variables standardized to 1 SD. Overall significance test  $P < 0.0001$  in all models. EIR = early insulin response at an OGTT ( $\Delta 0-30$  insulin/ $\Delta 0-30$  glucose). All models were adjusted for age at baseline.  $n = 47/667$ .

to determine the magnitude of the relationship to and the statistical significance of the predictors of the defined outcome (a 1-SD change in a log-transformed continuous variable corresponds approximately to a transition from the 50th to the 70th percentile in an unlogged continuous variable). In the multivariate models, separate analyses were made with adjustments for the possible confounding effects of BMI, as an indicator of obesity. In separate analyses, the WHR were used instead of BMI as an index of central obesity. To study possible multiplicative effects of significant predictors, interaction terms between significant predictors of type 2 diabetes were tested within the multivariate models. All analyses were adjusted for age at baseline and length of follow-up between investigations. The tertile limits of several factors were calculated in the

whole baseline population to get reliable estimates and were used in trend tests, using logistic regression, for the development of type 2 diabetes.

**RESULTS**— The incidence of type 2 diabetes during the course of the study was 7.0% (47 of 667) from 70 to 77 years of age.

Baseline clinical characteristics for the entire population and for subjects who did and did not develop type 2 diabetes (mean values and SD) and crude standardized odds ratios (ORs), are presented in Table 1. Intact and 32–33 split proinsulin, specific insulin, and IRI were significantly associated with the development of type 2 diabetes in the univariate analysis. The 32–33 split proinsulin showed the strongest relationship to the development of type 2 diabetes of the three spe-

cific measurements, as judged by the magnitude of the crude standardized ORs. The ratio between PLMs and insulin was not associated with the development of type 2 diabetes.

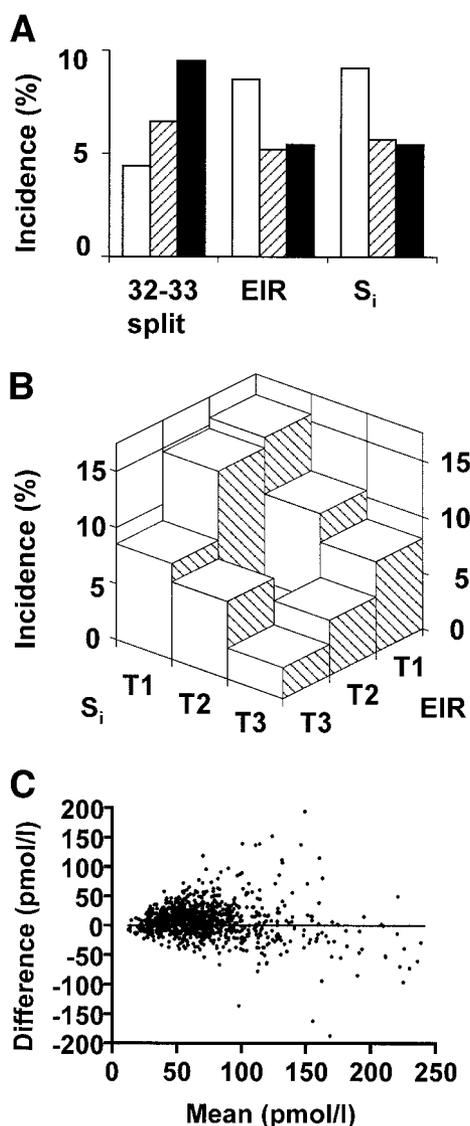
$S_i$ , but not the crude EIR, was associated with conversion to type 2 diabetes. However, after adjustment for  $S_i$ , EIR was associated with type 2 diabetes (Table 2, Model 1).

Figure 1A shows the unadjusted cumulative incidence of type 2 diabetes for the 7-year follow-up, by tertiles of 32–33 split proinsulin, EIR, and  $S_i$ . Trend test using logistic regression was significant ( $P < 0.001$ ) in all three cases.

Table 2 presents the results from seven multiple logistic regression models with type 2 diabetes as the outcome. EIR and  $S_i$  were significant predictors of the development of type 2 diabetes (Model 1). The 32–33 split proinsulin adjusted for insulin (Model 2) and intact proinsulin adjusted for insulin (Model 3) were also predictors for type 2 diabetes. When 32–33 split proinsulin (Model 4) or intact proinsulin (Model 5), one at the time, was added to the model including EIR and  $S_i$ , each was significantly associated with development of type 2 diabetes. Furthermore, adjustment of the observed associations for BMI and IGT, or for WHR and IGT, did not alter the significance of the associations neither between 32–33 split proinsulin (Model 6) or intact proinsulin (Model 7) and type 2 diabetes, respectively. Specific insulin was not associated with the development of type 2 diabetes when adjusted for  $S_i$  only (OR 1.10, 95% CI 0.86–1.41;  $P = 0.409$ ) or for 32–33 split proinsulin only (Model 2) or for intact proinsulin only (Model 3).

Figure 1B shows the incidence of type 2 diabetes for the 7-year follow-up by tertiles of EIR and tertiles of  $S_i$ . The graph suggests a multiplicative effect of a concurrent low EIR and a low  $S_i$ . Tests for interaction between EIR and  $S_i$  as predictors for type 2 diabetes in Model 1 using an interaction term in multiple logistic regression showed a borderline significant result (OR 0.90;  $P = 0.06$ ). Adding 32–33 split proinsulin to the model including the interaction term between EIR and  $S_i$  turned the association between the interaction term and the development of type 2 diabetes nonsignificant ( $P = 0.17$ ).

Correlation coefficients between  $S_i$  and 32–33 split proinsulin ( $r = -0.53$ ,  $P < 0.001$ ) and between  $S_i$  and specific



**Figure 1**—A: Incidence of type 2 diabetes over 7 years of follow-up, from age 70 years, in a population-based sample of 667 men by tertiles of fasting 32–33 split proinsulin concentrations, EIR at an OGTT, and  $S_i$  at a euglycemic insulin clamp. Filled columns represent the highest tertiles, and unfilled columns represent the lowest tertiles. T, tertiles. The limits for 32–33 split proinsulin concentrations were as follows: T1 <5.7 pmol/l, T2  $\geq$ 5.7 pmol/l or <10 pmol/l, and T3  $\geq$ 10 pmol/l. For EIR, the limits were T1 <16 pmol/mmol, T2  $\geq$ 16 pmol/mmol or <29 pmol/mmol, and T3  $\geq$ 29 pmol/mmol. For  $S_i$ , the limits were T1 <3.7, T2  $\geq$ 3.7 or <5.8, and T3  $\geq$ 5.8. B: Incidence of type 2 diabetes for the 7-year follow-up by tertiles of  $S_i$  and tertiles of EIR. C: Bland-Altman-plot. x-axis: mean value (pmol/l) of baseline IRI and the sum of true insulin, intact insulin, and 32–33 split proinsulin (specific determinations, in samples stored frozen since baseline). y-axis: Difference (pmol/l) between IRI and the specific determinations. There was no trend for the mean difference to rise or fall with increasing concentrations ( $r = -0.038$ ,  $P = 0.28$ ).

insulin ( $r = -0.62$ ,  $P < 0.001$ ) were higher compared with the correlation coefficients between EIR and 32–33 split proinsulin ( $r = 0.21$ ,  $P < 0.001$ ) and between EIR and specific insulin ( $r = 0.36$ ,  $P < 0.001$ ). The correlation coefficient between intact and 32–33 split proinsulin was high ( $r = 0.85$ ,  $P < 0.001$ ), and the correlation between 32–33 split proinsulin and specific insulin was moderate ( $r = 0.60$ ,  $P < 0.001$ ).

Figure 1C presents the result from the Bland-Altman plot, which showed good agreement between the determinations separated in time by  $\sim 5$  years without any range-specific deviations.

In the additional analysis, when type 2 diabetes was diagnosed based on the fasting glucose concentrations at baseline,

the results were found to be essentially the same as those shown above.

**CONCLUSIONS**— Both decreased  $S_i$  determined by the euglycemic insulin clamp and decreased EIR were predictors of type 2 diabetes in the multivariate analysis in this elderly male population, as has been shown previously in young Pima Indians (6). Furthermore, in the present study, the propeptides 32–33 split proinsulin and intact proinsulin significantly predicted conversion to type 2 diabetes over a 7-year follow-up, also after adjustments for the EIR and  $S_i$  determined by the gold standard euglycemic insulin clamp.

Hyperproinsulinemia can be a consequence of a primary reduction of insulin

secretion capacity. An increased proportion of proinsulin in secretory granules at the time of exocytosis may reflect a slower rate of conversion from proinsulin to insulin (26). It is assumed that the packaging of proinsulin and proinsulin conversion enzymes into the nascent secretory granules depends on an active sorting process (27), but studies on the specificity of the sorting process in the regulated secretory pathway have so far not shown conclusive results (27,28).

Proinsulin adjusted for insulin was a predictor for type 2 diabetes in contrast to the proinsulin-to-specific insulin (P:I) ratio. The former observation supports defective insulin processing, but the failure to find that the P:I ratio is not predictive does not necessarily support the contrary because the ratio contains a larger measurement error compared with proinsulin adjusted for insulin as a covariate, which will diminish its predictive power in regression analyses (29). Furthermore, use of a ratio to control for the denominator is only valid when the intercept of the regression of the numerator on the denominator is zero (29). For the P:I ratio, the intercept is higher than zero, which will introduce an overadjustment of the association between proinsulin and type 2 diabetes. Proinsulin concentrations may also be augmented by an increased demand placed on  $\beta$ -cells by hyperglycemia (30,31), i.e., secondary to insulin resistance (26). Therefore, one cannot entirely separate the roles of a pancreatic  $\beta$ -cell defect from the influence of insulin resistance when using proinsulin as a predictor of type 2 diabetes, without including measurements of these two characteristics in the same regression model. Our results show that both impaired EIR and insulin resistance precede the onset of type 2 diabetes and a synergistic effect on the outcome may be suggested (Fig. 1B); however, the interaction test was of borderline significance ( $P = 0.06$ ). But, proinsulin also predicted type 2 diabetes independent of these two characteristics and thus may reflect the synergistic effect of a biologic interaction between impaired EIR and insulin resistance better than how it is reflected by a calculated interaction term in the regression analyses. An interaction term, which will contain a higher measurement error than the included variables, will be disfavored in regression analyses. However, proinsulin predicted type 2 diabetes inde-

pendent of EIR and  $S_i$ , indicating that it may mirror some other defect present in the  $\beta$ -cells predisposing type 2 diabetes not expressed by the EIR or influenced by insulin resistance in the development of type 2 diabetes. The fasting proinsulin and insulin concentrations may be envisaged to reflect hepatic insulin resistance to a greater extent than insulin-mediated glucose uptake assessed with a euglycemic insulin clamp, which measures skeletal muscle glucose uptake at an insulin concentration at which hepatic glucose production is suppressed for most subjects. Proinsulin, as a marker of insulin resistance and  $S_i$ , may therefore partly assess different aspects of insulin resistance, which may explain that proinsulin turned out to be independent of  $S_i$  as a predictor of type 2 diabetes, a suggestion, however, that has to be tested in formal experiments.

The EIR was associated with conversion to type 2 diabetes only after adjustment for  $S_i$ . This result highlights the critical need for taking the degree of insulin resistance into account when investigating  $\beta$ -cell secretory dysfunction in relation to progressive impairment of glucose tolerance (32).

The prevalence of IGT at baseline was high, as could be expected with regard to the relatively high age of the participants. IGT was a powerful predictor of type 2 diabetes in terms of the crude OR, but adjustment for IGT in the multivariate models had no major impact on the observed associations between the propeptides and progression to type 2 diabetes. The observations that proinsulin concentrations already are elevated in the IGT state (33) and that proinsulin was a predictor of type 2 diabetes independent of IGT, indicate that hyperproinsulinemia and the pre-diabetic state of IGT are parallel phenomena.

Adjustment for BMI or WHR did not significantly affect any of the observed associations in the multivariate models between proinsulin and development of type 2 diabetes in our study, which is in line with that increased plasma proinsulin does not seem to be caused or affected by obesity (34). The relationship between specific insulin and development of type 2 diabetes was of borderline significance when adjusted for BMI in our study, which is consistent with previous reports (10,11).

Intact proinsulin and 32–33 split proinsulin were stronger predictors for type 2

diabetes than specific insulin. Considerably longer half-life of propeptides compared with insulin may lead to lower intraindividual variation (23). Therefore, the higher precision of point estimates of proinsulin measurements may contribute to their better predictive capacity for type 2 diabetes in comparison to measurements of specific insulin. However, if the higher precision of a point estimate contributes to the results from the regression models, one must assume that propeptides and specific insulin mediate or represent the same biologic effect on the outcome. The associations between 32–33 split proinsulin, intact proinsulin, and specific insulin, in descending order by their ORs, and the development of type 2 diabetes are consistent with results from earlier studies (14,15,35). However, the differences in the ORs for intact and 32–33 split proinsulin were modest, and the dividing line goes between the propeptides and specific insulin because it is not the plasma insulin concentrations per se but an increase in concentrations of its precursors that constitutes the association with type 2 diabetes. Therefore, the results from our own and other studies suggest that IRI assays, cross-reacting with proinsulin, overestimate the strength of the association between insulin, i.e., IRI and the development of type 2 diabetes.

Proinsulin is an independent predictor of coronary heart disease (36), and subjects with diabetes have an increased risk for coronary heart disease (37). Some subjects with the insulin resistance syndrome (38) from the original cohort examined in 1970–1973 are likely to have escaped follow-up at age 70 years (baseline) due to increased cardiovascular mortality. Therefore, the magnitude of the observed association between insulin resistance, proinsulin, and type 2 diabetes may be underestimated in the present study population, which represents a selection of survivors examined at 70 years of age. A limitation of this study was that it was performed only in men. However, in a study of elderly subjects, which included both nondiabetic men and women, proinsulin was more strongly and consistently associated with type 2 diabetes (35) than insulin.

We conclude that 32–33 split proinsulin and intact proinsulin were significant predictors of type 2 diabetes in this cohort, independent of the degree of in-

sulin resistance and the impaired insulin response, obesity, and glucose tolerance in contrast to specific insulin or IRI.

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