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LETTER

Comment on: Schmidt MI, Duncan BB, Vigo A et al (2006) Leptin and incident type 2 diabetes: risk or protection? Diabetologia 49:2086–2096

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To the Editor: We read with great interest the recently published paper by Schmidt et al., who prospectively investigated the association between leptin levels and incident diabetes in middle-aged adults in the Atherosclerosis Risk in Communities (ARIC) study [1]. We were intrigued by their results, which showed that high leptin levels predicted a lower risk of type 2 diabetes, once adjusted for factors purportedly associated with leptin resistance. Their results prompted us to perform similar analyses in the Hoorn Study. In this letter we would like to share our results, but also express some caution regarding the interpretation of the results.

The Hoorn Study is a population-based cohort study of glucose tolerance, which started in 1989 and included 2,484 white men and women aged 50 to 75 years [2]. An extensive physical examination took place and leptin was measured by means of a radioimmunoassay [3]. From 1996 to 1998 follow-up examinations were conducted [4]. Of the remaining 2,086 subjects who were invited, 1,513 subjects (72.5%) participated. After exclusion of subjects with type 2 diabetes at baseline and of subjects with missing data on leptin or covariates, prospective analyses were performed in 1,238 subjects (573 men and 665 women). The presence of type 2 diabetes at follow-up was ascertained by an OGTT, and defined according to the WHO 1999 criteria [5]. In addition, to make the study more comparable to the ARIC study, analyses were also performed using the diabetes definition according to the American Diabetes Association (ADA) 1997 criteria [6], which is based on fasting glucose levels only (86% of the cases were diagnosed on the basis of fasting glucose in the ARIC study [1]). Informed consent was obtained from all participants and ethical approval for the study was obtained from the local ethics committee.

The mean age at baseline was 60.1±6.9 years (60.0±6.9 years in men and 60.2±6.8 years in women), and median (interquartile range) leptin concentrations were 7.04 (2.99–15.16) μg/l (3.05 [1.66–5.34] μg/l in men, 13.68 [8.13–22.85] μg/l in women). After a mean follow-up of 6.4 years, 59 men and 57 women had developed type 2 diabetes according to the WHO 1999 criteria, and 51 men and 47 women had developed the disease according to the ADA 1997 criteria. Table 1 shows the results of logistic regression analyses, in which odds ratios for developing type 2 diabetes according to ADA 1997 are calculated. In women, but not in men, a positive statistically significant association was shown between leptin and incident diabetes, after adjustment for age (model 1). After adjustment for BMI, the difference between men and women disappeared and no association was observed in either sex (model 2). To study the individual influence of WHR and metabolic variables on the associations, we adjusted this model for these factors one by one (models 3 to 8). Finally, we added all variables to form one regression model, similarly to the approach of Schmidt et al. (model 9). In contrast to the results of Schmidt et al., the negative associations were not statistically significant and appeared more markedly in men, not in women.

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Table 1 Risk, for sex-specific tertiles of leptin, of developing type 2 diabetes according to the ADA 1997 criteria

	2nd tertile		3rd tertile		*p* value for trend
	OR	95% CI	OR	95% CI	
Men					
Model 1: age	1.06	0.52–2.17	1.11	0.55–2.26	0.101
Model 2: age + BMI	1.07	0.51–2.23	1.12	0.48–2.60	0.076
Model 3: age + BMI + WHR	0.91	0.43–1.92	0.85	0.36–2.01	0.287
Model 4: age + BMI + ln-insulin	0.99	0.47–2.09	0.90	0.38–2.14	0.202
Model 5: age + BMI + hypertension	1.04	0.50–2.18	1.06	0.45–2.46	0.124
Model 6: age + BMI + ln-triacylglycerol	0.93	0.44–1.96	0.91	0.39–2.15	0.110
Model 7: age + BMI + adiponectin	1.04	0.50–2.17	1.08	0.47–2.50	0.078
Model 8: age + BMI + fasting glucose	0.84	0.37–1.91	0.90	0.37–2.19	0.088
Model 9: all previous	0.69	0.30–1.61	0.59	0.23–1.55	0.304
Women					
Model 1: age	1.04	0.45–2.43	2.05	0.97–4.35	0.025
Model 2: age + BMI	0.80	0.34–1.93	1.14	0.46–2.83	0.541
Model 3: age + BMI + WHR	0.65	0.27–1.58	0.94	0.37–2.41	0.582
Model 4: age + BMI + ln-insulin	0.78	0.32–1.87	1.03	0.41–2.60	0.741
Model 5: age + BMI + hypertension	0.79	0.33–1.91	1.10	0.44–2.74	0.724
Model 6: age + BMI + ln-triacylglycerol	0.67	0.27–1.63	0.98	0.39–2.43	0.547
Model 7: age + BMI + adiponectin	0.73	0.30–1.76	1.01	0.40–2.54	0.939
Model 8: age + BMI + fasting glucose	0.93	0.37–2.36	1.11	0.40–3.05	0.702
Model 9: all previous	0.71	0.27–1.89	0.93	0.32–2.66	0.835

The first leptin tertile is the reference category. Values are odds ratios (ORs) with 95% CIs.

Table 2 shows the results of logistic regression analyses when incident diabetes was defined according to the WHO 1999 criteria. After adjustment for age, a significant positive association between leptin and incident diabetes was shown, particularly in women. Again, BMI largely explained this association. In the fully adjusted model,

Table 2 Risk, for sex-specific tertiles of leptin, of developing type 2 diabetes according to the WHO 1999 criteria

	2nd tertile		3rd tertile		*p* value for trend
	OR	95% CI	OR	95% CI	
Men					
Model 1: age	1.34	0.67–2.66	1.37	0.69–2.71	0.122
Model 2: age + BMI	1.36	0.67–2.75	1.42	0.64–3.17	0.112
Model 3: age + BMI + WHR	1.18	0.58–2.41	1.11	0.49–2.53	0.385
Model 4: age + BMI + ln-insulin	1.26	0.62–2.57	1.13	0.49–2.58	0.327
Model 5: age + BMI + hypertension	1.31	0.65–2.67	1.32	0.59–2.97	0.207
Model 6: age + BMI + ln-triacylglycerol	1.20	0.59–2.46	1.18	0.52–2.68	0.171
Model 7: age + BMI + adiponectin	1.33	0.66–2.69	1.38	0.62–3.08	0.119
Model 8: age + BMI + fasting glucose	1.17	0.55–2.53	1.18	0.51–2.75	0.153
Model 9: all previous	0.99	0.45–2.16	0.77	0.31–1.89	0.659
Women					
Model 1: age	1.42	0.64–3.14	2.63	1.27–5.44	0.010
Model 2: age + BMI	1.10	0.48–2.51	1.50	0.64–3.56	0.460
Model 3: age + BMI + WHR	0.92	0.40–2.13	1.30	0.54–3.14	0.484
Model 4: age + BMI + ln-insulin	1.06	0.46–2.41	1.32	0.55–3.20	0.725
Model 5: age + BMI + hypertension	1.09	0.48–2.49	1.46	0.61–3.48	0.602
Model 6: age + BMI + ln-triacylglycerol	0.91	0.39–2.12	1.28	0.54–3.06	0.465
Model 7: age + BMI + adiponectin	0.97	0.42–2.23	1.28	0.53–3.11	0.999
Model 8: age + BMI + fasting glucose	1.28	0.54–3.03	1.49	0.58–3.82	0.612
Model 9: all previous	0.94	0.38–2.32	1.20	0.45–3.19	0.864

The first leptin tertile is the reference category. Values are odds ratios (ORs) with 95% CIs.

higher leptin levels were associated with a slightly lower risk of type 2 diabetes in men, but not in women.

In the Hoorn Study, therefore, we were able to replicate—in men, but not in women—the findings of Schmidt et al. from the ARIC Study, when type 2 diabetes was defined on the basis of fasting glucose levels only. However, if incident type 2 diabetes was defined according to the WHO 1999 criteria, which also includes post-load glucose levels and is considered the gold standard for diagnosis of type 2 diabetes, there was no longer a strong negative association in men.

Schmidt et al. discuss the possibility of over-adjustment when adjusting for baseline glucose levels, because glucose may mediate part of the association, while other variables are considered to be true confounders. We argue, however, that controlling for other metabolic factors may also result in over-adjustment, because they also may well be mediators in the causal pathway by which high leptin leads to type 2 diabetes. The interpretation of the regression model that includes all these factors implies that a person with high leptin per BMI who does not develop insulin resistance, hypertension and metabolic abnormalities has advantages with respect to diabetes risk. It should, however, be realised that unfortunately most obese people do in fact develop these adiposity-related abnormalities. In addition, the results of the Hoorn Study, using data from the OGTT, suggest that the seemingly beneficial effect of high leptin after adjustment could also be an artefact due to imprecise measurement of diabetes.

In conclusion, we were not able to confirm the negative associations between leptin and incident diabetes when diabetes diagnosis was based on both fasting and post-load glucose levels (gold standard), and after adjusting for measures of obesity and metabolic factors. Although a weak negative association in men cannot be excluded, the adjustments for obesity and metabolic factors probably represent over-adjustment as a result of adjusting for mediating factors.

References

1. Schmidt MI, Duncan BB, Vigo A et al (2006) Leptin and incident type 2 diabetes: risk or protection? Diabetologia 49:2086–2096
2. Mooy JM, Grootenhuis PA, de Vries H et al (1995) Prevalence and determinants of glucose intolerance in a Dutch caucasian population. The Hoorn Study. Diabetes Care 18: 1270–1273
3. Ruige JB, Dekker JM, Blum WF et al (1999) Leptin and variables of body adiposity, energy balance, and insulin resistance in a population-based study. The Hoorn Study. Diabetes Care 22: 1097–1104
4. de Vegt F, Dekker JM, Jager A et al (2001) Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: The Hoorn Study. JAMA 285: 2109–2113
5. World Health Organisation (1999) World Health Organisation: Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation
6. No authors listed (1997) Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 20:1183–1197