

age groups. 165 (97%) of those who reported back pain indicated that their pain was in the lower lumbar region.

Participants reported that low back pain prevented them from doing key activities important in maintaining their homes and livelihoods. Common activities such as collecting water (figure 1), harvesting, and carrying heavy objects, including children, increased the risk of low back pain. DH observed that activities carried out at ground level, including sweeping the floor, washing clothes, and lifting loads (such as bricks, barley, or full water containers) onto the back were done with a flexed lumbar spine and little bending of the knees.

These findings show a high prevalence of low back pain in central Tibet, affecting more than a third of adults, which is a significantly higher prevalence than noted in the few reports from other low-income countries. Reduced function associated with low back pain is especially serious in marginal living conditions such as rural Tibet.

Because the survey was undertaken in the daytime, it could be argued that our participants, who were at home, might have been more likely to have low back pain than those at work, which would certainly be the case during harvest time. However, since we did the study before harvest time, most people were at home. The observation that ground level activities are done with little knee flexion is important in guiding the development of appropriate interventions.

As a result of the survey, township and city hospital doctors, who in turn trained village health workers, were trained in prevention and management of low back pain. The training included the principle of curve-reversal of the lumbar spine to reverse the effect of lumbar flexion, and the importance of the adaptation of activities to reduce the risk of low back pain. Posters and flip charts on back pain prevention prepared by local artists were distributed to rural clinics.

A Back-Happy Tap-Stand was designed and installed in more than 30 villages (figure 2). The stand reduces the need for lumbar flexion by adding a high tap and waist-high bench to water collection points, removing the necessity of having to bend when filling and lifting water containers.

Low back pain is a significant, under recognised problem in central Tibet, impairing health and productivity, and is likely to be a problem in many rural societies combining poor economic conditions with subsistence farming. Longitudinal studies are needed to assess the effect of cost-effective and sustainable interventions to reduce the burden of low back pain. Health and development assistance projects should expand beyond communicable diseases to include conditions such as low back pain.

#### Contributors

All authors contributed to study design and writing of the report. D Hoy also collected, analysed, and interpreted data. M J Toole also helped interpret data.

#### Conflict of interest statement

None declared.

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## Adiponectin and protection against type 2 diabetes mellitus

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**Adiponectin is an adipocyte-derived peptide, which has anti-inflammatory and insulin-sensitising properties. We designed a nested case-control study to assess whether baseline adiponectin concentrations in plasma are independently associated with risk of type 2 diabetes. We found that adiponectin concentrations in plasma were lower among individuals who later developed type 2 diabetes than among controls (mean 5.34  $\mu\text{g}/\text{mL}$  [SD 3.49] vs 6.87  $\mu\text{g}/\text{mL}$  [4.58],  $p < 0.0001$ ). High concentrations of adiponectin were associated with a substantially reduced relative risk of type 2 diabetes after adjustment for age, sex, waist-to-hip ratio, body-mass index, smoking, exercise, alcohol consumption, education, and glycosylated haemoglobin A<sub>1c</sub> (odds ratio 4th vs 1st quartile 0.3 [95% CI 0.2–0.7],  $p = 0.0051$ ). We conclude that adiponectin is independently associated with a reduced risk of type 2 diabetes in apparently healthy individuals.**

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Adiponectin<sup>1</sup> is exclusively and abundantly expressed in white adipose tissue and has been shown to have insulin-sensitising and anti-inflammatory properties.<sup>2,3</sup> A diabetes-susceptibility locus has been mapped to human chromosome 3q27, where the adiponectin gene is located. Thus, both genetic and functional data suggest that adiponectin could be involved in the pathogenesis of type 2 diabetes. Additionally, decreased concentrations of adiponectin have been shown to precede the onset of disease in an animal model of diabetes. Alternatively, high concentrations of adiponectin might prevent the onset of type 2 diabetes.

We designed a prospective, nested case-control study within the population-based EPIC (European Prospective Investigation into Cancer and Nutrition) Potsdam cohort, which includes 27 548 individuals, to assess whether baseline concentrations of adiponectin in plasma independently modify the risk of type 2 diabetes in apparently healthy individuals. All participants gave informed consent and the study was approved by the ethics committee of Landesärztekammer-Brandenburg, Germany. Participants (age 35–65 years at baseline) were recruited from the general population between 1994 and 1998, and were asked to complete self-administered questionnaires and to undergo a computer-guided interview by trained personnel. Anthropometric measurements (height and weight, waist and hip circumference) were taken, and body-

mass index (BMI) and waist-to-hip ratio (WHR) were calculated. Peripheral venous blood samples were taken, citrate was added, and they were centrifuged at 1000 *g* for 10 min at 4°C. Plasma was removed and stored at -80°C. Adiponectin concentrations were measured by radioimmunoassay (Linco Research, St Charles, MI, USA), and glycosylated haemoglobin A<sub>1c</sub> by enzyme immunoassay (DAKO Diagnostika, Hamburg, Germany). Diabetes-associated antibodies GAD65 and IA-2 were analysed by radioimmunoassay (Medipan Diagnostica, Selchow, Germany).

Follow-up questionnaires were mailed 2–3 years later. Potential cases of incident diabetes (ie, individuals with type 2 diabetes at follow-up but not at baseline) were identified by self-report. Each potential incident case was verified by the patient's primary-care physician. Only individuals with medically confirmed diabetes were included in the study. Analysis of diabetes-associated antibodies GAD65 and IA-2 left 192 medically and biochemically confirmed cases of type 2 diabetes. Each of the individuals with confirmed type 2 diabetes were matched for age and sex with two control individuals from the basic cohort. The non-parametric Mann-Whitney *U* test was used to analyse differences in continuous variables between cases and controls, and the Mantel-Haenszel test was used to test for differences in proportions. Unconditional logistic regression analysis was used to estimate odds ratios and corresponding 95% CIs. Analyses were done with SAS software, version 8.0 (SAS Institute, Cary, NC, USA), and SPSS software, version 8.0.

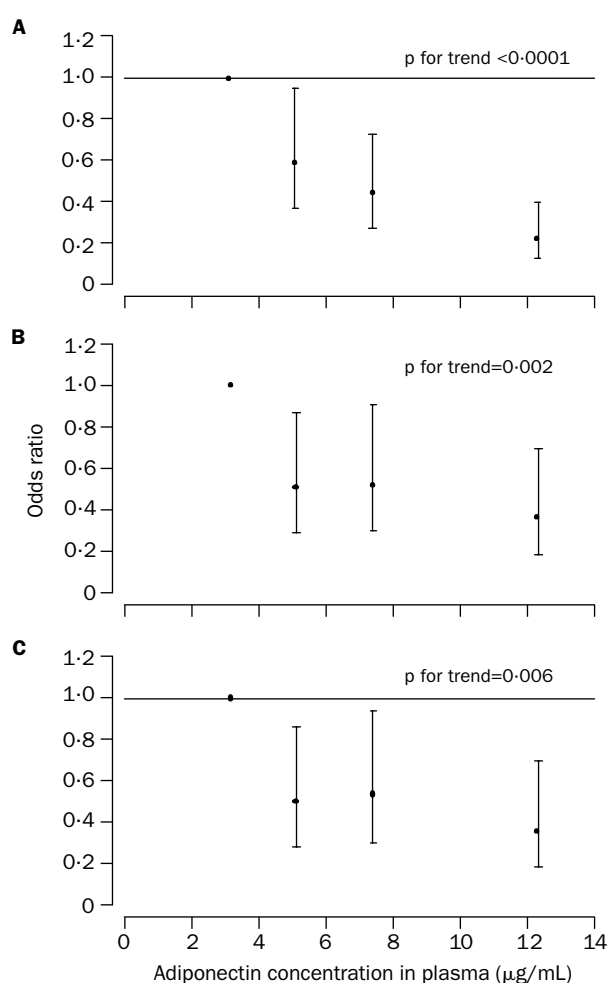
We identified 192 individuals with medically confirmed incident type 2 diabetes, who were matched with 384 controls. Individuals with missing values for one of the variables being used in the statistical models were excluded (cases *n*=5; controls *n*=8), leaving 187 cases and 376 controls for the final analysis. The main baseline characteristics of individuals with incident type 2 diabetes and controls are summarised in the table. The mean adiponectin concentration was significantly lower in individuals with incident type 2 diabetes than in controls.

Increasing concentrations of adiponectin were associated with a lower risk of subsequent type 2 diabetes when concentrations were analysed both by quartile (figure) and as a continuous variable (odds ratio 0.90 [95% CI 0.84–0.97], *p*=0.0068, in the fully adjusted model). Assuming a certain number of undiagnosed prevalent cases of type 2 diabetes in a middle-aged western population, and to reduce the confounding of results by undetected cases of prevalent type 2 diabetes at baseline, we repeated all analyses including only individuals with a glycosylated haemoglobin A<sub>1c</sub> value below 6.0%. 90 (96%) of the participants with a glycosylated haemoglobin A<sub>1c</sub> below 6% and available fasting blood samples had a fasting plasma glucose concentration below 7.0 mmol/L. Therefore, the number of individuals with

	Cases ( <i>n</i> =187)	Controls ( <i>n</i> =376)	<i>p</i>
BMI (kg/m <sup>2</sup> )	30.1 (4.8)	26.4 (3.5)	<0.0001
WHR	0.94 (0.09)	0.89 (0.09)	<0.0001
Sport (h/week)	0.5 (1.1)	0.9 (1.6)	0.007
Alcohol consumption (g/day)	7.5 (28.3)	10.5 (16.4)	0.456
Adiponectin (µg/mL)	5.34 (3.49)	6.87 (4.58)	<0.0001
Haemoglobin A <sub>1c</sub> (%)	6.39 (2.16)	4.73 (0.72)	<0.0001
Age (years)	56 (7)	56 (7)	*
Men	110 (59%)	221 (59%)	*
Current smokers	36 (19%)	79 (21%)	0.658
Hypertension	147 (79%)	194 (52%)	<0.0001
Hyperlipoproteinaemia	79 (43%)	118 (31%)	0.005
Less than high school education	83 (44%)	142 (38%)	0.033

Data are mean (SD) or number (%). \*Age and sex were matching variables.

#### Baseline characteristics of study cohort



#### Risk of subsequent type 2 diabetes according to the respective median of ascending quartiles of adiponectin concentrations in plasma

A: adjusted for age and sex; B: adjusted for age, sex, body-mass index, and waist-height ratio; C: adjusted for all clinical variables including glycosylated haemoglobin A<sub>1c</sub>. Error bars represent 95% CIs. Horizontal line at 1.0 represents reference line. Participants were divided into quartiles according to adiponectin concentration in plasma. Quartile cut points were determined from the combined group of controls and cases.

prevalent diabetes at baseline was small within this restricted analysis. Results of this subgroup were similar to those in all individuals, irrespective of whether we used adiponectin as quartiles (odds ratios [95% CIs] for increasing quartiles: 1.00 [reference], 0.67 [0.34–1.35], 0.56 [0.27–1.15], and 0.36 [0.16–0.86] in the fully adjusted model; *p* for trend 0.02) or as a continuous variable (risk reduction of 8.1% per µg/mL, *p*=0.021, in the fully adjusted model).

Women had a higher mean adiponectin concentration than men (*p*<0.0001). To investigate effect modification by sex, we calculated odds ratios after sex stratification, which yielded slightly stronger risk estimates with increasing quartiles of adiponectin for women compared with men (odds ratios for increasing quartiles: 1.0, 0.5, 0.4, and 0.3 for women and 1.0, 0.6, 0.5, and 0.4 for men in the fully adjusted model).

We have shown an association between adiponectin concentrations in plasma and risk of type 2 diabetes in apparently healthy individuals. Our results suggest that adiponectin has a substantial role in the pathogenesis of type 2 diabetes, and that adiponectin could be used as an indicator of risk in addition to the established risk parameters such as obesity and physical activity. Although adiponectin

seems to be implicated in the development of insulin resistance and  $\beta$ -cell function, explicit mechanisms linking adiponectin and incident type 2 diabetes remain speculative.<sup>2,4</sup> Genetic polymorphisms might be involved in the regulation of adiponectin concentrations in plasma, especially taking into account the existing linkage in the region of the adiponectin gene with type 2 diabetes. Unfortunately, information about family history of diabetes, which would reflect genetic influence, was not available in our cohort. Furthermore the precise time-course of adiponectin concentrations in plasma during development of type 2 diabetes remains to be elucidated.

In conclusion, we found that increased concentrations of adiponectin are strongly and independently associated with reduced risk of incident type 2 diabetes in apparently healthy individuals. Our results accord with those of a study in Pima Indians.<sup>5</sup> Both observations, combined with emerging functional and genetic evidence, support the concept that adiponectin has a central role in the development of type 2 diabetes.

#### Contributors

J Spranger contributed to protocol design, biochemical analysis, statistical analysis, and writing of the manuscript; A Kroke was involved in protocol design, data collection, outcome assessment, and statistical analysis; M Möhlig helped with protocol design, biochemical analysis, statistical analysis, and writing of the manuscript; M M Bergmann was involved in data collection and outcome assessment; M Ristow contributed to biochemical analysis and writing of the manuscript; H Boeing helped with data collection, outcome assessment, statistical analysis, and writing of the manuscript; and A F H Pfeiffer was involved in protocol design, statistical analysis, and writing of the manuscript. All contributors reviewed the final report.

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## A tumour that secretes glucagon-like peptide-1 and somatostatin in a patient with reactive hypoglycaemia and diabetes

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**Glucagon-like peptide 1 (GLP-1), an insulinotropic hormone normally synthesised in the intestinal mucosa and released in response to a meal, is essential for normal glucose homeostasis. There is much interest in the use of GLP-1 to treat diabetes, since the risk of hypoglycaemia is thought to be low. We report an instance of a 45-year-old woman with a GLP-1 and somatostatin secreting neuroendocrine tumour who presented with reactive hypoglycaemia and hyperglycaemia, but who was subsequently cured by surgery. This case, of a neuroendocrine tumour secreting GLP-1 and causing reactive hypoglycaemia, indicates a potential adverse effect of GLP-1 therapy for diabetes.**

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Glucagon-like peptide-1 (GLP-1), an insulinotropic hormone, is normally synthesised in the intestinal mucosa by tissue-specific post-translational processing of the glucagon precursor, proglucagon. The peptide is essential for glucose homeostasis and is released into the circulation after a meal to enhance insulin secretion. Here we describe a patient with a GLP-1 and somatostatin secreting neuroendocrine tumour, causing reactive hypoglycaemia and diabetes, respectively.

The 45-year-old woman presented with a 7-month history of episodes of dizziness and sweating with difficulty expressing herself, and appearing vague. These episodes resolved with dextrose tablets. Home blood-glucose monitoring revealed fluctuating concentrations of glucose, between 1 mmol/L and 30 mmol/L. Results of a 75 g oral glucose tolerance test indicated a fasting blood glucose of 8.1 mmol/L, but a 2-h value of 1.9 mmol/L during which the patient was symptomatic. The woman was prescribed metformin and guar gum, but her blood sugar concentrations continued to fluctuate between 14 mmol/L and 2.0 mmol/L. During these hypoglycaemic episodes, the patient was symptomatic.

During a 72-h fast she did not develop hypoglycaemia, excluding an insulinoma. At the end of the fast, her blood glucose was 7.8 mmol/L. Within 1 h of eating she developed symptomatic reactive hypoglycaemia with a plasma glucose of 1.8 mmol/L. Her blood concentrations of plasma insulin and C-peptide were inappropriately raised at 285 mU/L (normal range <3.0 mU/L) and more than 4000 pmol/L (<300 pmol/L), respectively. Urine and plasma sulphonylurea screens were negative. Fasting plasma concentrations of somatostatin and chromogranin B were raised at 4000 pmol/L (<150 pmol/L) and 181 pmol/L (<150 pmol/L), respectively. Somatostatin (<sup>111</sup>indium-pentetreotide) receptor scintigraphy revealed dense tracer uptake in the pelvis (see webfigure 1 at <http://image.thelancet.com/extras/02let6005webfigure1.pdf>), and a pelvic CT scan showed a 12×11×12 cm encapsulated right-sided pelvic mass (see webfigure 2 at <http://image.thelancet.com/extras/02let6005webfigure2.pdf>). We therefore diagnosed a pelvic neuroendocrine tumour.

We did a 5-h oral glucose tolerance test and collected samples for measurement of glucose, insulin, C-peptide, somatostatin, and GLP-1 (figure 1A). The fasting blood glucose concentration was 10 mmol/L and increased to a delayed peak (17 mmol/L) at 90 min. Somatostatin