

High Levels of Education Are Associated With an Increased Risk of Latent Autoimmune Diabetes in Adults

Results from the Nord-Trøndelag Health Study

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OBJECTIVE — To investigate whether the risk for autoimmune diabetes in adults differs between socioeconomic groups and to compare such risk with that for type 2 diabetes.

RESEARCH DESIGN AND METHODS — The inhabitants of the Norwegian county of Nord-Trøndelag were investigated by questionnaires and clinical examinations on three occasions during 1984–2008. We used information from a subset consisting of 56,296 subjects (participating in at least two surveys), including 122 incident cases of autoimmune diabetes in adults (aged ≥ 35 and anti-GAD positive) and 1,555 cases of type 2 diabetes (aged ≥ 35 and anti-GAD negative). Hazard ratios (HRs) of diabetes associated with self-reported education and occupation were estimated by Cox proportional hazards models.

RESULTS — High levels of education (university versus primary school) were associated with an increased risk of autoimmune diabetes (HR 1.98 [95% CI 1.21–3.26]), after adjustment for BMI, lifestyle factors, and family history of diabetes. Case subjects with high levels of education had lower levels of C-peptide, tended to have higher levels of anti-GAD, and were more often treated with insulin. Conversely, these subjects had a reduced risk of type 2 diabetes (HR 0.69 [95% CI 0.57–0.82]), a risk that was partly explained by lower BMI and more physical activity (adjusted HR 0.89 [95% CI 0.74–1.06]).

CONCLUSIONS — High levels of education are associated with an increased risk of autoimmune diabetes in adults, a finding that may be mediated by effects on autoimmune activity. Because the association is not explained by traditional risk factors, other, currently unidentified, environmental factors are likely to be involved.

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There is some evidence indicating that socioeconomic conditions during early life can affect the incidence of autoimmune diabetes. Lower rates of childhood diabetes have been reported in more materially deprived areas, and children in families with a high socioeconomic position seem more prone to develop type 1 diabetes (1–3). It has been

hypothesized that these associations result from differences in environmental factors, such as feeding patterns, hygiene standards, and lack of infections in early life, conditions that may affect the immune system and trigger an autoimmune reaction (4,5). Whether socioeconomic factors associate with autoimmune diabetes that develops at adult age is, however,

not known. Contrasting with data on childhood type 1 diabetes, the risk of developing type 2 diabetes is more pronounced in lower socioeconomic groups (6–8). This association can be explained, at least in part, by traditional risk factors such as overweight and physical inactivity (9).

Autoimmune diabetes in adults comprises latent autoimmune diabetes in adults (LADA) as well as “classical” type 1 diabetes. Autoimmunity is indicated by the presence of antibodies against β -cell-associated antigens, such as GAD (10). LADA is by far the most common form of adult-onset autoimmune diabetes and is estimated to account for 2–12% of all diabetes cases (11). As indicated by the name, onset of LADA is slower than type 1 diabetes, and insulin treatment is typically not required at the time of diagnosis. Even though it is characterized by autoimmunity, LADA patients also display features of type 2 diabetes with risk associations to being overweight and physical inactivity (12).

The aim of this study was to investigate whether the risk of developing autoimmune diabetes in adults differs between socioeconomic groups and to compare such risk with that for type 2 diabetes. Furthermore, we aimed to analyze whether evidence could be found for a role of autoimmunity and whether associations found could be explained by traditional risk factors for type 2 diabetes, such as family history of diabetes, being overweight, physical inactivity, or smoking.

RESEARCH DESIGN AND METHODS

HUNT1

All inhabitants aged ≥ 20 years of the Norwegian county of Nord-Trøndelag ($n = 85,100$) were invited to take part in the first Nord-Trøndelag Health Study (HUNT) survey (HUNT1) in 1984–1986 (Fig. 1). The survey featured clinical examinations (including measurements of height, weight, and blood pressure) and questionnaires with questions on several

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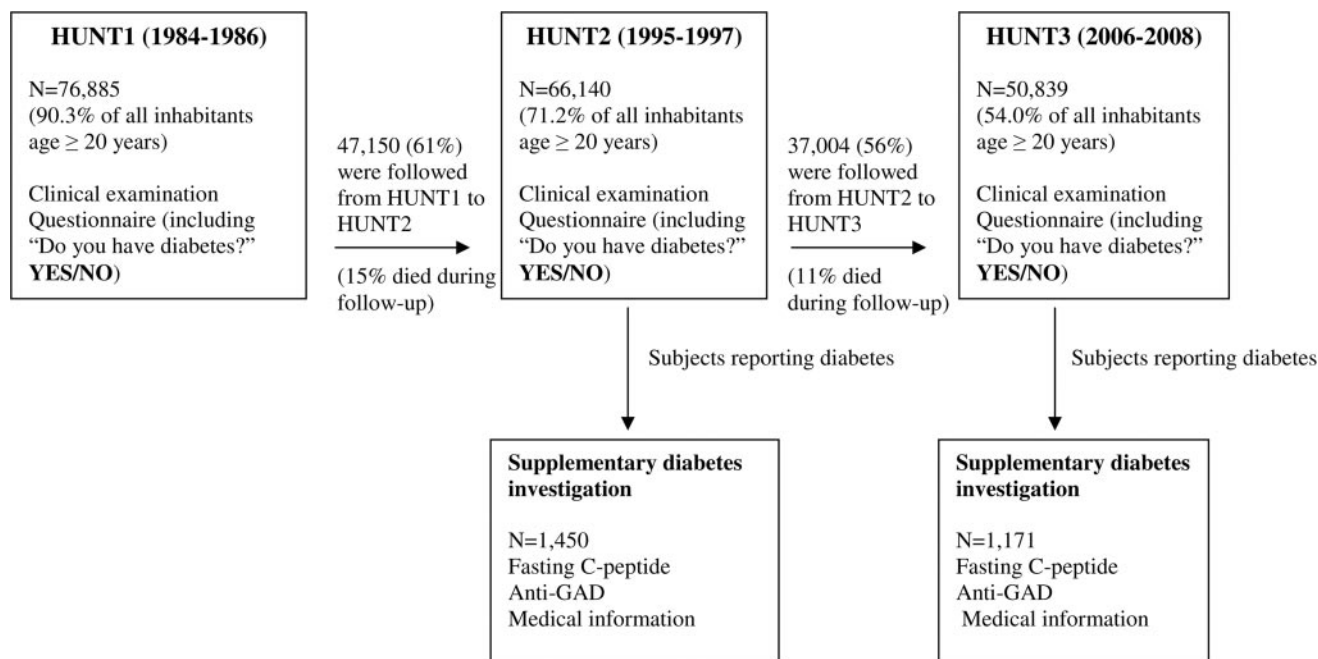


Figure 1—The Nord-Trøndelag Health Study (HUNT), 1984–2008.

diseases (including diabetes), education, occupation, lifestyle, and family history of diabetes. A total of 90.3% of those invited participated ($n = 76,885$) (13).

HUNT2

A second, similar health survey was conducted in 1995–1997 (HUNT2), again including all inhabitants aged ≥ 20 years ($n = 92,936$). In this follow-up investigation, the response rate was 71.2% ($n = 66,140$) (14). Among those participating in HUNT1, 61% ($n = 47,150$) also participated in HUNT2.

HUNT3

A third health survey, with similar design, was conducted in 2006–2008 (HUNT3). A total of 94,194 individuals were invited to this second follow-up of the inhabitants of the Nord-Trøndelag County. The response rate was 54% ($n = 50,839$). Among those participating in HUNT2, 56% ($n = 37,004$) participated in HUNT3, and of those participating in HUNT1, 40% ($n = 30,754$) also participated in HUNT3.

An overview of the whole HUNT study is given in Fig. 1. Our study population included subjects who participated in at least two of three health surveys (i.e., they were followed for a minimum of 11 years) and who did not have known diabetes at baseline and for whom complete baseline information on age, sex, and education was available ($n = 56,296$). The

HUNT was approved by the regional medical research ethical committee and the Norwegian Data Inspectorate. The participants gave informed consent.

Identification of diabetes

In the HUNT, cases of diabetes were identified by questionnaire. In our study population, 2,461 incident cases of diabetes were identified during the 22-year follow-up (1,119 at HUNT2 and 1,342 at HUNT3). Subjects with self-reported diabetes were invited to a supplementary investigation where questionnaire information on medical history and treatment was checked and fasting levels of C-peptide and anti-GAD were determined. Information on anti-GAD was available for 96% of the cases in this study population at HUNT2 (for 19% of these through analyses of blood samples from the HUNT Biobank, collected at the time of the HUNT2 clinical investigation, as described previously [15]) and, because of nonparticipation in the supplementary diabetes investigation, for 56% of diabetes cases identified at HUNT3. In total information on anti-GAD and age at onset of diabetes was available for 1,729 (70%) of the original 2,461 incident cases identified in our study sample.

Classification of diabetes

Subjects aged ≥ 35 years at diagnosis and anti-GAD positive (≥ 0.08) were classified as having autoimmune diabetes with

adult onset but without the need for insulin treatment at diabetes onset (i.e., LADA, or "classical" type 1 diabetes; $n = 122$ in all). Subjects aged ≥ 35 years at diagnosis and who were anti-GAD negative (< 0.08) were classified as having type 2 diabetes ($n = 1,555$). A total of 52 subjects did not fit these criteria and were therefore not included in the analyses of this article. A second definition was used to exclude cases of type 1 diabetes from LADA cases. By this definition, anti-GAD-positive patients aged ≥ 35 years at diagnosis were classified as having LADA only if they reported that insulin treatment was started the year after the year of diagnosis ($n = 96$). Anti-GAD-positive subjects aged ≥ 35 years without information on insulin treatment ($n = 10$) or with insulin treatment from the year of diagnosis ($n = 16$) (i.e., cases of type 1 diabetes) were thus excluded.

Measurements of anti-GAD and C-peptide

Anti-GAD and fasting C-peptides were analyzed in samples of serum at the Hormone Laboratory of Aker University Hospital (Oslo, Norway). Anti-GAD was analyzed by an immunoprecipitation radioligand assay based on a previously validated method (16). Sensitivity was 0.64 and specificity 1.00 at the cut off level of > 0.08 (by the Diabetes AutoAntibody Standardization Program DASP [17]). Anti-GAD values are reported in World

Health Organization (WHO) units (0.08 = 43 WHO units/ml, as recommended) (18). At HUNT2, analysis of C-peptide was done by radioimmunoassay (Diagnostic System Laboratories, Webster, TX) and at HUNT3 by a noncompetitive immunofluorimetric assay applying a DELFIA kit (PerkinElmer Life Sciences, Wallac Oy, Turku, Finland).

Education and occupation

In the HUNT1 and the HUNT2 questionnaires, participants were asked to specify their highest level of education. There were eight (HUNT1) or five (HUNT2) response options, ranging from primary school to ≥ 4 years of college or university. In the analyses, these responses were collapsed into three categories: low (primary school), middle (upper secondary school), and high (university level) education. Participants in HUNT1 and HUNT2 were also asked to classify themselves in one of nine occupational categories. The occupational categories were reclassified according to an approximation of the international Erikson, Goldthorpe, and Portocarero social class scheme (19) and divided into three groups; low (unskilled or skilled manual workers), middle (nonmanual employees, farmers, fishermen, and other self-employed), and high (higher- and lower-grade professionals, administrators, and officials). Individuals who reported that they had not been gainfully employed (because of, for example, full-time housework, studies, or disability pension) were excluded ($n = 3,371$). A full description of these questions and response options can be found in supplementary Table 1 in the online appendix (available at <http://care.diabetesjournals.org/cgi/content/full/dc10-1061/DC1>).

Covariates

Based on measures of height and weight from the clinical investigations at HUNT1 and HUNT2, BMI was calculated as weight in kilograms divided by the square of height in meters. Questionnaire information on physical activity, alcohol consumption, and smoking was used to classify subjects as 1) physically active or inactive; 2) as abstainers, occasional, low, moderate, and high consumers of alcohol; and 3) as never, former, or current smokers. Information on history of diabetes in the family, measured by separate questions on diabetes in parents, siblings, children, and age at onset for each relative, was available from the HUNT2 questionnaire.

Table 1—Characteristics of the study participants at HUNT1 (1984–1986) and HUNT2 (1995–1997) by educational level

	Primary school	Upper secondary school	University
HUNT1 1984–1986			
<i>n</i> (%) subjects	23,214 (57.7)	12,669 (31.5)	4,349 (10.8)
Mean age (years)	50.5 \pm 13.5	37.0 \pm 12.4	40.4 \pm 11.1
Men (%)	42.1	53.0	55.3
Mean BMI kg/m ²	25.5 \pm 3.9	24.2 \pm 3.3	24.0 \pm 3.0
BMI ≥ 30 kg/m ² (%)	11.8	5.3	3.7
Physically inactive (%)	41.8	39.9	28.2
Smokers (%)	35.3	35.4	20.6
Family history of diabetes (%)	19.3	15.2	17.1
HUNT2 1995–1997			
<i>n</i> (%) subjects	20,853 (39.7)	21,798 (41.5)	9,826 (18.7)
Mean age (years)	60.6 \pm 14.0	45.5 \pm 14.3	45.1 \pm 12.8
Men (%)	40.9	51.5	47.0
Mean BMI kg/m ²	27.1 \pm 4.2	26.1 \pm 3.9	25.6 \pm 3.6
BMI ≥ 30 kg/m ² (%)	21.6	14.2	10.4
Physically inactive (%)	30.9	23.7	15.6
Smokers (%)	32.0	31.6	18.4
Family history of diabetes (%)	18.9	14.5	14.4

Data are means \pm SD, unless otherwise indicated.

Statistical analyses

Cox proportional hazards models (SAS 9.2 Phreg procedure; SAS Institute, Cary, NC) were used to estimate hazard ratios (HRs) and corresponding 95% CIs of autoimmune diabetes in adults and type 2 diabetes associated with education and occupation. Person-years of follow-up were accumulated from age at start of the study (either at HUNT1 or HUNT2) until age at diagnosis of diabetes, age at death, or age at the end of follow-up (either at HUNT2 or HUNT3), whichever came first. Age (in years) was used as the underlying time scale in the Cox model. HRs are presented both with adjustment for only age and sex and with additional adjustment for BMI, physical activity, smoking, alcohol consumption, and family history of diabetes (will be referred to as adjusted HR in the results section). The lowest exposure category was used as a reference in all analyses, unless otherwise stated. The analyses were time dependent, which means that for subjects with information on education and occupation or any of the covariates from more than one point in time, information was updated during follow-up.

RESULTS

Duration of follow-up

Of 56,296 subjects included in our analyses, 48% were followed for 11 years and 52% for 22 years, yielding a total of 862,789 person-years of follow-up. The

mean duration of follow-up was 15.3 years.

Baseline characteristics

Table 1 displays participants at HUNT1 and HUNT2 according to educational level. There was a shift upwards in the distribution of education between the two surveys, but the differences in characteristics of subjects with high and low education were seen at both surveys (i.e., subjects with high levels of education were younger, less overweight, more physically active, and smoked less compared with subjects with low education).

Education, occupation, and risk of autoimmune diabetes and type 2 diabetes

High levels of education (i.e., university level) were associated with an increased risk of autoimmune diabetes compared with a primary-school education (Table 2). Conversely, there was a reduced risk of type 2 diabetes for subjects with high levels of education. The negative association with type 2 diabetes was, to a large extent, explained by differences in BMI and lifestyle, whereas adjustment for these factors actually strengthened the association with autoimmune diabetes. For both autoimmune diabetes and type 2 diabetes, similar results were seen for men and women (results not shown). Similar, although slightly less pronounced, results were seen when socioeconomic position

Table 2—HRs of autoimmune diabetes in adults and type 2 diabetes associated with education: results from the HUNT 1984–2008

Education	Person-years	Autoimmune diabetes in adults			Type 2 diabetes		
		Cases (n)	Adjusted for age and sex HR (95% CI)	Adjusted for age, sex, BMI, lifestyle,* and family history of diabetes HR (95% CI)	Cases (n)	Adjusted for age and sex HR (95% CI)	Adjusted for age, sex, BMI, lifestyle,* and family history of diabetes HR (95% CI)
Primary school	305,328	74	1	1	995	1	1
Upper secondary school	237,458	21	0.61 (0.37–1.01)	0.60 (0.35–1.02)	408	0.88 (0.78–0.99)	0.98 (0.87–1.12)
University	97,706	27	1.60 (1.00–2.56)	1.98 (1.21–3.26)	152	0.69 (0.57–0.82)	0.89 (0.74–1.06)

*Physical activity, smoking, and alcohol consumption.

was measured by occupation (e.g., high occupational position [higher- and lower-grade professionals] was associated with an adjusted HR of 1.53 [95% CI 0.82–2.84] for LADA and 0.87 [0.73–1.03] for type 2 diabetes).

The lowest risk of autoimmune diabetes was seen in the middle educational category. Compared with this category (rather than to primary school) the adjusted HR of autoimmune diabetes was 1.68 (95% CI 0.98–2.88) in subjects with low education and 3.33 (1.81–6.13) in subjects with high levels of education.

Education, occupation, and risk of LADA

When the analyses were restricted to cases of LADA (after exclusion of subjects with insulin treatment starting from the year of diagnosis), we ended up with similar results but with fewer cases ($n = 96$, 79% of all autoimmune cases). The ad-

justed HR of LADA was 1.68 (95% CI 0.93–3.05) for subjects with high versus low education and 1.57 (0.77–3.22) for those reporting high versus low occupational position.

HUNT1 to HUNT2 and HUNT2 to HUNT3 analyzed separately

We also analyzed the data as two separate cohorts (i.e., HUNT1 to HUNT2 [1984–1997] and HUNT2 to HUNT3 [1995–2008]). In both cohorts, high levels of education were associated with an increased risk of autoimmune diabetes (adjusted HR 2.64 [95% CI 1.41–4.97] and 4.03 [1.47–11.04], respectively). A decreased risk of type 2 diabetes associated with high levels of education, before adjustment for BMI and lifestyle, was also seen in both cohorts (HR 0.66 [95% CI 0.49–0.91] and 0.75 [0.59–0.96], respectively).

Characteristics of cases by educational level

Cases of autoimmune diabetes with high levels of education were more often treated with insulin, had longer duration of diabetes and lower levels of C-peptide, and tended to have higher levels of anti-GAD compared with those with low education (Table 3). Conversely, there were no clear differences between cases of type 2 diabetes with high versus low education with regard to insulin treatment, duration of diabetes, or levels of C-peptide.

CONCLUSIONS

Main findings

The main finding of this study was that high levels of education were associated with increased risk of autoimmune diabetes in adults. This is in contrast with the reduced risk of type 2 diabetes in subjects with high socioeconomic position re-

Table 3—Characteristics of autoimmune diabetes in adults and type 2 diabetes cases by educational level: results from the HUNT 1984–2008

	Autoimmune diabetes in adults				Type 2 diabetes			
	Primary School	Upper secondary school	University	P	Primary School	Upper secondary school	University	P
n cases	74 (61)*	21 (17)*	27 (18)*		995	408	152	
Age at baseline	57.7 ± 10.1	48.3 ± 10.4	50.4 ± 10.1	0.0017	57.6 ± 10.1	50.3 ± 11.0	51.0 ± 10.2	<0.0001
Age at onset	63.7 ± 9.8	53.9 ± 10.4	55.4 ± 10.3	0.0003	63.6 ± 10.3	57.0 ± 10.9	57.5 ± 10.0	<0.0001
Insulin treatment (%)	32.8	55.0	56.0	0.0456	16.4	16.0	12.9	0.2951
Duration of diabetes (years)	7.3 ± 7.0	9.3 ± 6.3	10.4 ± 6.9	0.0520	7.2 ± 6.4	6.6 ± 6.0	6.9 ± 6.0	0.5596
Anti-GAD (WHO units/ml)	276 ± 314	325 ± 293	363 ± 320	0.1967	—	—	—	—
C-peptide (pmol/l)	637.0 (705.0)	511.0 (695.0)	217.0 (746.0)	0.0004	842.5 (615.0)	901.0 (578.0)	825.0 (502.0)	0.5286

Data are means ± SD or median (IQR) for C-peptide (since C-peptide was not normally distributed), unless otherwise indicated. P values for differences between university level and primary school were calculated with *t* test (means), χ^2 test (proportions), and Kruskal-Wallis test (medians). *Number of LADA cases.

ported in this and previous studies (6–8). The association with type 2 diabetes was, to a large extent, explained by differences in BMI and lifestyle, but these factors did not explain the association between high levels of education and autoimmune diabetes. Instead, there was an association with reduced β -cell function, with lower levels of C-peptide, more frequent use of insulin, and a tendency for higher levels of anti-GAD. These observations indicate effects linked to β -cell destruction by autoimmunity and are in line with some (1,2), but not all (20), previous reports on type 1 diabetes in children.

Mechanisms

Given an effect by socioeconomic conditions on autoimmune diabetes, what are the possible mechanisms? Associations with childhood diabetes could plausibly be explained by “the hygiene hypothesis,” which assigns importance to a lower prevalence of infections early in life (4), and/or by differences in dietary habits (5,21). Educational level may be influenced by socioeconomic position during childhood and adolescence (22), and a high level of education could thus be reflective of a high socioeconomic position during childhood. We speculate that childhood environment, in which factors such as low prevalence of early infections, could have been operative on mechanisms of autoimmunity, can affect the evolution of autoimmune diabetes several decades later in life. Such a notion would be supported by signs of autoimmunity (i.e., antibodies, long before onset of diabetes). Preliminary analyses of incident cases of LADA in the HUNT3 survey do show GAD antibodies in the vast majority of blood samples taken 11 years earlier at HUNT2 (V. Grill, personal communication). However, we lack information on antibody positivity close to childhood in our LADA patients. Importantly, the possibility that other, currently unidentified, environmental factors associated with socioeconomic factors during adult age are operative cannot be excluded.

Could the association be U shaped?

There was a tendency for a U-shaped relationship between education and autoimmune diabetes with an increased risk also in subjects with low education; such results thus being similar to those for type 2 diabetes. This may be explained by the fact that LADA seems to share some features with type 2 diabetes, including insulin resistance (12,23). These findings

should, however, be interpreted with caution as they were based on small numbers, and no U-shaped relationship was seen when occupation was used to measure socioeconomic position.

Methodological considerations

Cases of diabetes were identified by self-report. If undiagnosed diabetes was more common in subjects with low socioeconomic position, this method may lead to an overestimation of the association between high levels of education and diabetes. If this was the case, we would expect the association between type 2 diabetes and low education to be attenuated. Notably, our findings regarding type 2 diabetes were consistent with previous reports (6–8). We did find that cases with low education were less likely to participate in the supplementary diabetes investigation aimed at classifying cases according to type of diabetes. In the third HUNT, nonparticipation was 44% among cases, and selection bias may certainly have influenced the results. However, the association with autoimmune diabetes was still present when the analyses were restricted to follow-up data from HUNT2, where 96% of the self-reported diabetes cases were classified according to type. Socioeconomic position was measured by self-reported information on education and occupation. Education is an important indicator of socioeconomic situation (22), and in our study it had the advantage of allowing us to classify a larger proportion of subjects than occupation including those who study and those who are unemployed. This self-reported information may be crude, but because this is a prospective study we can assume that any misclassification is nondifferential and therefore will tend to dilute the associations rather than result in overestimations of HRs.

This study indicates that high levels of education are associated with an increased risk of autoimmune diabetes, a finding that may be mediated by effects on autoimmune activity. The association is not explained by traditional risk factors, which suggests that other, currently unidentified, environmental factors are likely to be involved.

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L.O. contributed to developing the objective of the study and interpretation of results, analyzed data, and was responsible for writing the manuscript. A.A. contributed to the interpretation of results and reviewed/edited the manuscript. V.G. contributed to development of the objective of the study and interpretation of results and reviewed/edited the manuscript. K.M. researched data and reviewed/edited the manuscript. S.C. contributed to development of the objective of the study and interpretation of results and reviewed/edited the manuscript.

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