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# Adult-Onset Autoimmune Diabetes is Largely due to Modifiable Risk Factors: Results from the Norwegian HUNT Study

**Bahareh Rasouli[1]*, Tomas Andersson[1], Valdemar Grill[2], Kristian Midthjell[3], Lisa Olsson[1,4] and Sofia Carlsson[1]**

[1]*Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Sweden*

[2]*NTNU Institute of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, and Trøndheim University Hospital, Norway*

[3]*HUNT Research Centre, Department of Community Medicine and General Practice, Norwegian University of Science and Technology, Norway*

[4]*Centre for Health Equity Studies, Stockholm University/Karolinska Institute, Sweden*

## Abstract

**Introduction:** Adult-onset autoimmune diabetes is prevalent, yet there are limited data on risk factors.

**Aim:** Our aim was to examine how combinations of modifiable lifestyle factors are associated with risk of adult-onset autoimmune diabetes and to estimate the Population Attributable Risk (PAR) related to such factors.

**Methods:** We used incidence data from Nord-Trøndelag Health Survey Study (HUNT), a large population-based study where adults aged ≥ 20 years old were investigated in three consecutive surveys during 1984-2008 (n=49,712; eligible for this study). Among self-reported diabetes patients, presence of Glutamic Acid Decarboxylase Antibodies (GADA) and age at onset ≥ 35 years old were used to identify incident cases of adult-onset autoimmune diabetes (n=164). Hazard Ratios (HR) of autoimmune diabetes by lifestyle factors were estimated by Cox regression and PAR were calculated for single items and combination of lifestyle factors.

**Results:** A reduced risk of adult-onset autoimmune diabetes was conferred by BMI<25, physical activity, regular alcohol consumption and psychosocial well-being. Positivity for all four healthy lifestyle factors gave a HR of 0.10 (95% CI=0.02-0.40) compared with no positivity. Estimation of PAR indicated that 69% (CI=45-79%) of all cases of adult-onset autoimmune diabetes could be prevented through these factors with BMI< 25 as the most important contributor (PAR for BMI ≥ 25= 34%, CI=20-48%).

**Conclusions:** Provided that these associations are causal, then the majority of adult-onset autoimmune diabetes cases are preventable by modification of common lifestyle factors primarily by maintaining a BMI in the non-overweight range.

**Keywords:** Epidemiology; Autoimmune diabetes; Lifestyle risk factors; Population attributable risk

**Abbreviations:** GADA: Glutamic Acid Decarboxylase Antibodies; HR: Hazard Ratios; PAR: Population Attributable Risk

## Introduction

It is well-known that the risk of type 2 diabetes can be reduced by lifestyle modification including; normal weight [1], regular physical activity [2], moderate alcohol consumption [3], healthy diet [4], and by refraining from smoking [5]. Estimation of population attributable risks (PAR) suggests that 72% to 91% of type 2 diabetes cases can thereby be prevented [4,6,7]. To what extent lifestyle modification may have a preventive potential with regard to other forms of diabetes, is however largely unexplored.

Adult-onset autoimmune diabetes may be the second most common form of diabetes, accounting for 2-12% of all cases of diabetes [8]. It is often sub-grouped into classical type1 diabetes and latent autoimmune diabetes in adults (LADA), the most frequent form of autoimmune diabetes in adults, which compared to classical type 1 diabetes, progresses more slowly and requires insulin treatment at a later stage [9,10].

To date, there are few studies on risk factors for autoimmune diabetes in adults [11-15] and as far as we know, no investigations on the preventive potential of a healthy lifestyle in this form of diabetes. Additional research also needs include the interaction of lifestyle factors with family history of diabetes (FHD). The relative lack of studies on risk factors may be attributable to the fact that in most observational studies, cases of adult-onset autoimmune diabetes cannot be separated from cases of type 2 diabetes due to lack of information on indicators of autoimmunity such as antibodies against glutamic acid decarboxylase–GADA.

One exception is the Nord-Trøndelag Health Study (HUNT) Study, a population-based study providing data on ~50,000 individuals that can be followed prospectively with regard to onset and form of diabetes. We used data from HUNT to investigate the risk of adult-onset autoimmune diabetes in relation to the combination of modifiable risk factors and estimated PAR related to these factors.

## Materials and Methods

### Study population

The design and recruitment for the HUNT Study are described in detail previously [16]. Briefly, the HUNT Study consists of three

***Corresponding author:** Bahareh Rasouli, Unit of Epidemiology, Institute of Environmental Medicine (IMM), KarolinskaInstitutet, 171 77 Stockholm, Sweden, Tel: + 46 8 524 87430; Fax: + 46 8 31 39 61; E-mail: bahareh.rasouli@ki.se

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consecutive health surveys conducted in 1984-1986 (HUNT1), 1995-1997 (HUNT2), and 2006-2008 (HUNT3). At all three occasions, the entire adult population aged ≥20 years in the Nord Trøndelag County in Norway was invited to participate. The surveys comprised self-administrated questionnaires with items on health and lifestyle, clinical examinations, and blood sampling (the latter only in HUNT2 and HUNT3). The overall participation rates of HUNT1, HUNT2, and HUNT3 were 90.3% (n=76,885), 71.3% (n=66,140), and 54% (n=50,839), respectively. The HUNT Surveys have been conducted according to regulations from the Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics, including informed consent from participants.

Based on these three cross-sectional surveys, we formed a cohort consisting of individuals who participated in at least two surveys (HUNT1, HUNT2, and/or HUNT3). The study population which formed the basis of our analyses included 49,712 (799,506 person-years) men and women who were free of diabetes at baseline and for whom complete information on age, sex, lifestyle factors, and covariates of interests were available (HUNT1 or HUNT2), with follow-up information on onset of diabetes for 11 (HUNT1-HUNT2) or 22 years (HUNT1-HUNT3).

## Identification of adult-onset autoimmune diabetes cases

At the follow-up investigations in 1995-97 and 2006-2008, i.e. HUNT2 and HUNT3, persons with incident diabetes were identified by questionnaire and were invited to an additional investigation. This included collection of fasting blood samples for analyses of serum GADA, C-peptide and glucose as well as information on diabetes duration, and treatment. Based on this information we classified patients as having adult-onset autoimmune diabetes if they were GADA positive (≥0.08 antibody index) with age at onset ≥35 years old (n=164; ~7% of all cases of diabetes; in this study we excluded type 2 diabetes (GADA negative) and other types of diabetes from the analyses).

## Biochemical analysis

Fasting serum levels of GADA and C-peptide (RIA, Diagnostic System Laboratories, Webster, TX) were analysed at Aker University Hospital, Hormone Laboratory, Oslo, Norway as described earlier [16]. GADA levels were expressed as an antibody index value relative to standard serum [17]. A cut-off value of >0.08, corresponding to 43 WHO units/ml [18] was considered positive by Aker Hormone Laboratory based on the data from the Diabetes Autoantibody Standardization Program (DASP). As calculated by DASP 2003, the cut-off of >0.08 was chosen for the assay to ensure the highest possible specificity (1.00) with a yielded sensitivity of 0.64 [19].

| Characteristics [a] | Individuals not reporting diabetes | Adults with autoimmune diabetes |
|---|---|---|
| No. of subjects | 49712 | 164 |
| Age at baseline, mean, y (SD) | 50 (17) | 53 (11) |
| % Men | 47 | 49 |
| % with university education | 14 | 20 |
| BMI, mean, kg/m$^2$ (SD) | 25.5 (3.8) | 29.1 (5.0) |
| % Overweight (BMI ≥ 25) | 39 | 41 |
| % Obese (BMI ≥ 30) | 12 | 38 |
| % Physical inactivity | 33 | 42 |
| % Heavy smokers | 7 | 5 |
| %With FHD | 33 | 55 |
| WHR, mean (SD) [b] | 0.84 (0.08) | 0.87 (0.07) |
| %With History of High Blood Pressure [b] | 18 | 16 |
| Triglycerides, mean, mmol/l [b] | 1.71 (1.06) | 2.40 (2.25) |
| HDL-cholesterol, mean, mmol/l [b] | 1.39 (0.39) | 1.29 (0.37) |
| Cholesterol, mean, mmol/l [b] | 5.92 (1.24) | 6.08 (1.29) |

[a]Baseline characteristics from either HUNT1 or HUNT2, depending on when the participant entered the study
[b]The information is only available from HUNT2-HUNT3 (1995-2008)

**Table 1:** Baseline characteristics of subjects with autoimmune diabetes and without diabetes: results from HUNT study (1984-2008).

## Assessment of risk factors

Baseline information on lifestyle factors and other covariates was collected from the surveys in 1984-86 and 1995-97 (HUNT1 or HUNT2). Anthropometric measurements included weight measured to the nearest 0.5 kg, and height to the nearest 1.0 cm. Body mass index (BMI) was calculated as body Weight (Kg)/(height (m))$^2$ and categorized according to WHO definitions (normal:<25, overweight:25-30, obese:≥30 kg/m$^2$) [20]. Waist and hip circumferences were measured only at HUNT2 and HUNT3 (data were thus only available for follow-up at HUNT3), from which a waist to hip ratio (WHR) was calculated. Sex-specific cut-off points (≥0.90 for men, and ≥0.85 for women) as defined by WHO were used to classify in risk groups [21]. Questionnaire information was used to classify subjects according to smoking status (never and ever smoking). Ever smokers were categorized into light (<20 cigarettes/day) and heavy smokers (≥ 20 cigarettes/day). Information on frequency of alcohol over the last 14 days was collected by the self-administrated questionnaire. Information on amounts of alcohol consumption at baseline, enabling calculating grams of intake per day, was available only at HUNT2 (data were thus only available for follow-up form 199-1997 to 2006-2008), and were therefore not used in the combined score. Information of intensity and frequency of physical activity was used to classify participants into three groups: active, moderately active, and inactive. Psychosocial well-being was assessed by five multiple choice questions related to calmness, cheerfulness, life satisfaction, nervousness, and subjective sense of vigour; a total score ranging from 5 to 29 was calculated and categorized into quartiles (very high: 5-9, high: 10-11, moderate: 12-14, and low: ≥ 15). Absence of sleep disturbances and psychosocial well-being (score <15) were considered as desirable psychosocial status [15]. Information on presence of family history of diabetes in any first and second degree relatives was obtained from questionnaires at baseline or from follow-up.

## Classification of low risk categories

A specific aim was to assess the preventive potential of a combination of modifiable lifestyle factors. To this end variables were dichotomized to yield a low-risk category for each variable. Healthy lifestyle categories were defined based on public health recommendations [20] as well as on evidence from previous studies on the associations of individual lifestyle factors [12,14,15]. One point was awarded for each factor in the "healthy" range, i.e. normal BMI (<25 kg/m$^2$), regular physical activity, desirable psychosocial status, regular (but moderate) alcohol consumption (Supplementary Table 1). Since smoking did not increase risk in adult-onset autoimmune diabetes [11], refraining from smoking was not included in analyses as a healthy lifestyle factor.

## Statistical analysis

Cox proportional hazards models using age as the underlying time metric were used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for incidence of adult-onset autoimmune diabetes (SAS 9.2, SAS Institute Inc, Cary, NC, USA). Calculation of person-years started from the age at entry into the study (HUNT1 or HUNT2), and

ended at age of diabetes onset, death, or age at the end of follow-up (HUNT2 [1995-1997], or HUNT3 [2006-2008]), whichever occurred first.

The first stage of analysis focused on modelling factors that confer a risk of adult-onset autoimmune diabetes. Multivariable models were adjusted for, sex, FHD, BMI, educational level, physical activity, and smoking. To estimate biological interaction between FHD and each lifestyle factor we calculated attributable proportion (AP) due to interaction as AP=RERI/HR++, and synergy index S=[HR++ -1]/[(HR+- -1)+(HR-+ -1)] [22].

In the secondary analysis we treated the healthy lifestyle score as an ordinal variable, using the category believed to be the least healthy (zero score) as the reference group. We also calculated the *P*-values for the linear trend of ln (HR) (results presented in Figure 2). Third, we examined the risk of adult-onset autoimmune diabetes in relation to the specific combinations of healthy lifestyle factors, defined as participants with healthy lifestyle for each factor compared with all other participants as the comparison group. To analyse how risk of adult-onset autoimmune diabetes differs we added each factor to the combined score of healthy lifestyle factors (Table 3). The material used in simultaneously analysis (no missing data on all lifestyle factors of interest) encompassed 106 adult-onset autoimmune diabetes cases.

We calculated the PAR to estimate the proportion of cases in the population that would have been prevented if all participants adopted the healthy lifestyle for single lifestyle factor and also combinations of lifestyle factors, assuming a causal relationship between these lifestyle factors and risk of autoimmune diabetes. It was calculated using the formula p(HR-1)/(1+p[HR-1]), where p is prevalence of individuals in high risk group and HR is corresponding adjusted hazard ratio and also 95% CIs for the PARs [23].

## Results

### Baseline characteristics

Table 1 show participants characteristics in patients with autoimmune diabetes and individuals without diabetes. Subjects who developed adult-onset autoimmune diabetes tended to be older, heavier, having higher frequency of FHD, having higher university education background, and more physically inactive compared to those who did not develop diabetes.

The supplementary table 2 shows participants characteristics by number of healthy risk factors. Participants with more than one healthy lifestyle factor tended to be younger, have higher education, and were less likely to have an unfavourable plasma lipid profile and high WHR.

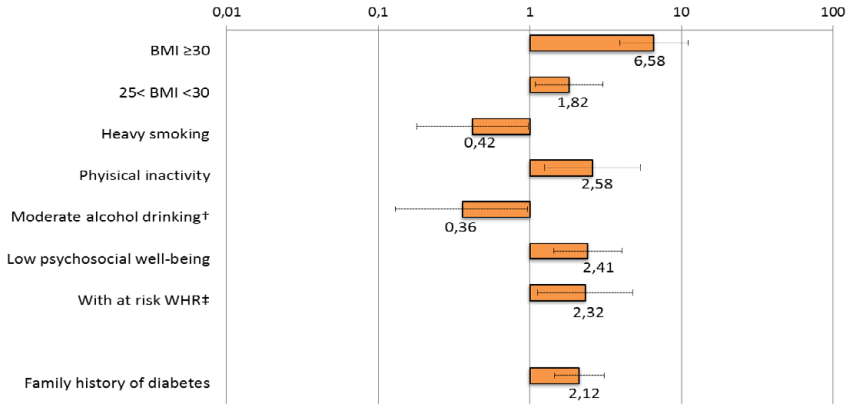
### Risk of adult-onset autoimmune diabetes in relation to individual lifestyle factors and FHD

Figure 1 depicts the main effect of the lifestyle factors and FHD

| Lifestyle risk factors (risk factor B) | No. Cases | Person-years | HR [a] (95% CI) FHD but not risk factor B | HR [a] (95% CI) Risk factor B but not FHD | HR [a] (95% CI) FHD and risk factor B | SI (95% CI) | AP (95% CI) |
|---|---|---|---|---|---|---|---|
| Overweight (25 ≤ BMI<30) | 47 | 323,793 | 2.23 (1.00-4.99) | 1.38 (0.65-2.94) | 4.60 (2.32-9.10) | 2.23 (0.70-7.04) | 0.43 (0.03-0.83) |
| Obesity (30 ≤ BMI) | 48 | 90,072 | 2.16 (0.97-4.84) | 6.69 (3.25-13.77) | 11.68 (5.68-24.01) | 1.56 (0.81-3.01) | 0.33 (0.00-0.72) |
| WHR (at risk) [b] | 18 | 69,193 | 2.15 (0.86-5.35) | 1.84 (0.61-5.55) | 5.75 (2.24-14.74) | 2.39 (0.63-9.08) | 0.48 (0.01-0.95) |
| Physical inactivity | 74 | 484,696 | 2.13 (1.31-3.45) | 1.28 (0.71-2.28) | 3.62 (2.13-6.14) | 1.85 (0.74-4.67) | 0.33 (0.00-0.71) |
| Non-regular alcohol consumption | 73 | 299,414 | 2.40 (1.33-4.33) | 1.32 (0.70-2.51) | 3.68 (2.02-6.70) | 1.56 (0.64-3.79) | 0.26 (0.00-0.69) |
| Low psychosocial well-being | 22 | 80,490 | 1.58 (0.90-2.76) | 1.53 (0.69-3.42) | 5.03 (2.56-9.89) | 3.63 (0.86-15.25) | 0.58 (0.24-0.93) |

SI: Synergy Index; AP: Attributable Proportion
Total study population: N=49,712.
[a] All combinations adjusted for age and sex; smoking, education, physical activity, and BMI (except the factor under analyses)
[b] Results from HUNT2 to HUNT3 (1995-2008)

**Table 2:** Interaction effects on adult-onset autoimmune diabetes of Co-exposure to FHD and lifestyle risk factors (risk factor B).




Grams of alcohol consumption were categorized according to quartiles; moderate alcohol intake defined as 2-7g/d; follow-up 1997-2008
Information on WHR was only available from HUNT2 in 1997, and could thus only be assessed for follow-up 1997-2008.

**Figure 1:** HRs of adult-onset autoimmune diabetes in relation to lifestyle factors and FHD: results from HUNT Study (1984-2008). Adjusted for age, sex, BMI, FHD, education, physical activity, and smoking (except for the factor under analysis).

on risks for adult-onset autoimmune diabetes. In multivariable survival analysis, the following factors were associated with risk of adult-onset autoimmune diabetes: overweight (HR=1.82, 95% CI=1.09-3.04), physical inactivity (HR=2.58, 95% CI=1.25-5.36), heavy smoking (HR=0.42, 95% CI=0.18-0.98), alcohol drinking (HR=0.36, 95% CI=0.13-0.97 (2-7 g/day), low psychological wellbeing (HR=2.41, 95% CI=1.44-4.05), and FHD (HR=2.12, 95% CI=1.45-3.10). The PAR for adult-onset autoimmune diabetes attributable to obesity was 34% (95% CI=20-48); this was by far the largest PAR among all lifestyle factors.

## Interaction between FHD and lifestyle factors

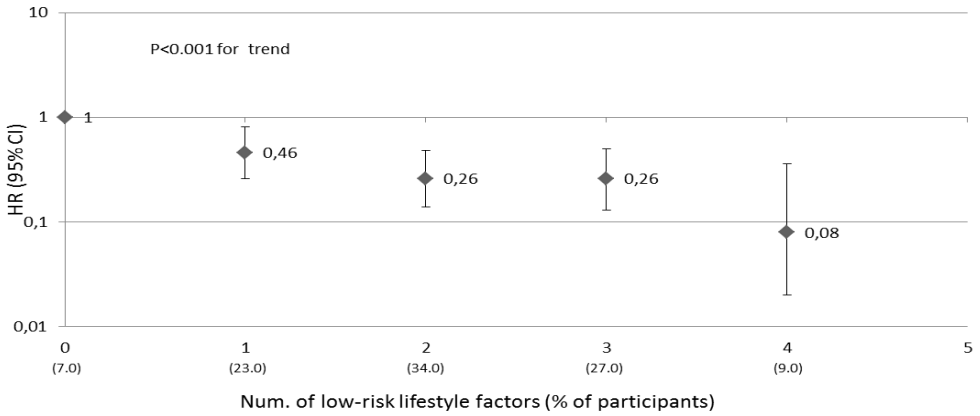
The lifestyle risk factors were also studied in relation to FHD. Effects were additive with HRs ranging from 3.62(for physical inactivity and FHD) to 11.68 (for obesity and FHD) but no significant interaction between FHD and lifestyle risk factors could be detected (Table 2).

## Combinations of healthy lifestyle factors

The risks of autoimmune diabetes in adults by number of healthy lifestyle factors are presented in Figure 2. The healthy lifestyle score was inversely associated with risk of adult-onset autoimmune diabetes (P for trend, <0.001). Each additional lifestyle factor in the low risk group indicated a 42% risk reduction for adult-onset autoimmune diabetes (HR=0.58, 95% CI=0.48-0.70). Compared with the least healthy lifestyle score (0 points), the HRs for adult-onset autoimmune diabetes ranged from 0.46 (CI=0.26-0.81) in subjects with one low-risk factor to 0.08 (CI=0.02-0.36) in subjects with four healthy lifestyle factors (4 points).

We also evaluated the risk among participants with specific combinations of healthy lifestyle factors (Table 3). In individuals who reported regular alcohol consumption and psychosocial well-being a 30% reduced risk came out. In those who in addition had BMI ≤25, the risk tended to be reduced by 53% and in 3 of 5 new cases appeared attributable to not adhering to these three healthy lifestyle factors. Adding regular physical activity, a 75% (CI=0.06-1.01) reduced risk was seen. Estimation of PAR indicated that 69% (95% CI=45-79%) of the cases of adult-onset autoimmune diabetes was attributable to being in the unhealthy group for all four of the lifestyle factors.

Stratifying these analyses by FHD suggested that having four healthy lifestyle factors was associated with a similarly reduced risk of adult-onset autoimmune diabetes in subjects with FHD (HR=0.22, 95% CI=0.03-1.64), and without FHD (HR= 0.28, 95% CI=0.04-2.05). Our findings also suggest a preventive potential of adult-onset autoimmune




Low-risk lifestyle factors included regular physical activity, regular alcohol consumption (>1time/14days), BMI (<25 kgm$^{-2}$), psychosocial well-being. Adjusted for age (years), sex (male vs. female), smoking (never, light or heavy smokers), education (primary school, upper secondary school or university), and FHD (presence of any FHD vs. absence of FHD)

**Figure 2:** HRs of adult-onset autoimmune diabetes according to the number of low-risk lifestyle factors, results from HUNT study (1984-2008).

| No. of healthy lifestyle factors | No. Cases Exposed/non-exposed (n/n) | Among all 49,712 Participants In low risk group/all other not in low risk group (%) | HR [a] (95% CI) | Population attributable risk [b] (95% CI), % |
|---|---|---|---|---|
| **2 healthy lifestyle factors** Regular alcohol intake psychosocial well-being | 26/80 | 35/65 | 0.70 (0.43-1.13) | 36 (1-56) |
| **3 healthy lifestyle factors** Regular alcohol intake psychosocial well-being BMI<25 | 7/99 | 18/82 | 0.47 (0.22-1.04) | 63 (42-77) |
| **4 healthy lifestyle factors** Regular alcohol intake Psychosocial well-being Regular physical activity BMI<25 | 2/104 | 9/91 | 0.25 (0.06-1.01) | 69 (45-79) |

a Adjusted for age (years), sex (male vs. female) and FHD (presence of any FHD vs absence of FHD), smoking (never, light or heavy smokers), education (primary school, upper secondary school or university), and each lifestyle risk factors not already included in the model. Compared with all other participants not in this low-risk group.
b The population attributable risk is the percentage of cases in the population that would theoretically not have occurred if all participants had been in low-risk category for the specific set of lifestyle factors.

**Table 3:** HR of adult-onset autoimmune diabetes and population attributable risk according to healthy lifestyle factors: results from HUNT study (1984-2008).

diabetes in normal as well as in overweight subjects with three healthy lifestyle factors; HR 0.45 (95% CI=0.10-1.95) vs. 0.77 (95% CI=0.39-1.54), respectively.

We compared median levels of C-peptide and GADA in low vs. high risk categories on individual and combined lifestyle factors. The most consistent findings were in cases with BMI <25 vs. ≥25 where levels of C-peptide were 58% (CI=0.25-0.71) lower (153 vs. 698 [median]) (Figure 3), and levels of GADA was almost two times (CI=0.82-4.63) higher (0.54 vs. 0.16 [median]).There was also on average 50% (CI=0.25-1.03) lower levels of C-peptide for those with three or four healthy lifestyle factors, compared to those with none (386 vs. 847[median]) (Figure 4).

## Discussion

In this large prospective study in men and women from Norwegian HUNT Study, we estimate that 69% of adult-onset autoimmune diabetes cases could be prevented by adhering to a healthy lifestyle including,

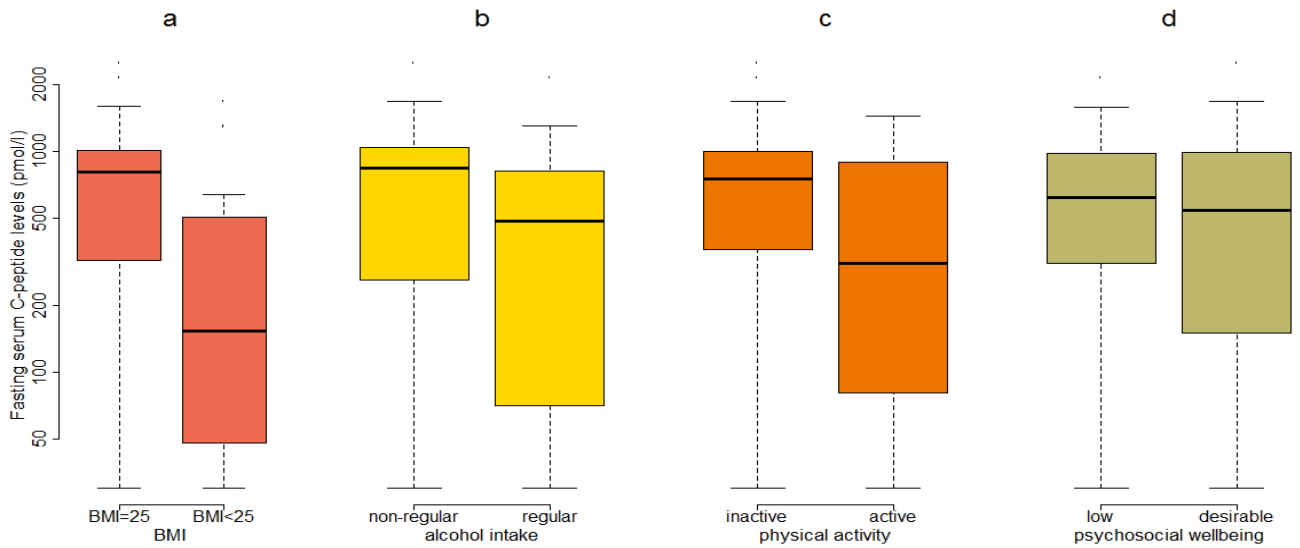



**Figure 3:** Box-plot of medians of fasting serum C-peptide level (pmol/l) in autoimmune diabetic patients in low-risk and high-risk lifestyle groups; (a) BMI, (b) Alcohol intake, (c) Physical activity, (d) psychosocial well-being. Results from HUNT study (1984-2008).

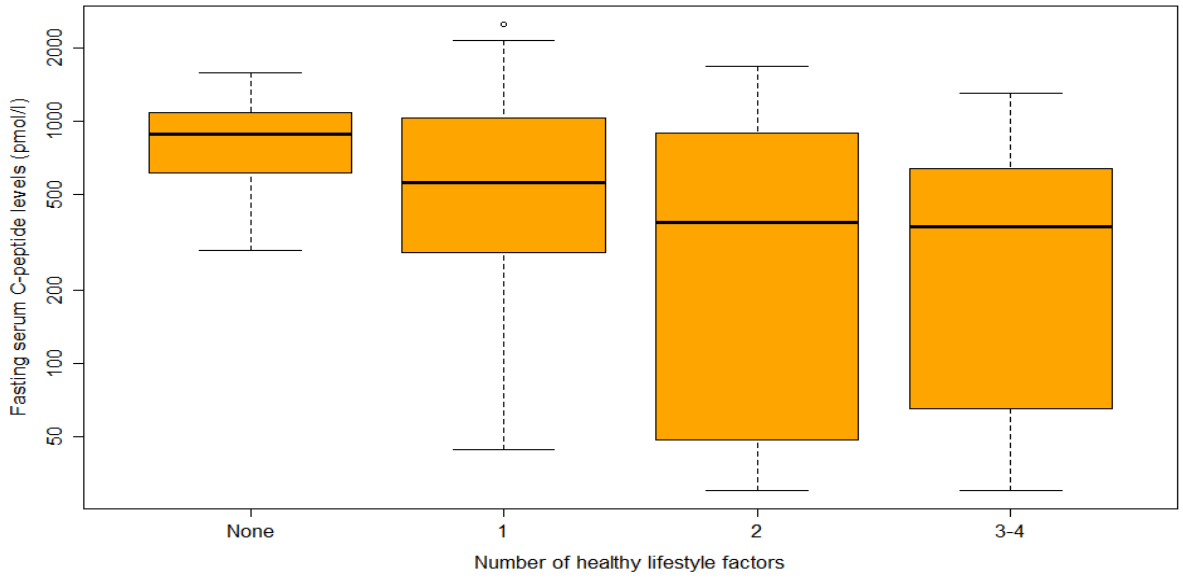



**Figure 4:** Box-plot of medians of fasting serum C-peptide level (pmol/l) in autoimmune diabetic patients according number of healthy lifestyle factors; results from HUNT study (1984-2008).

BMI ≤ 25, psychosocial well-being, and regular physical activity and alcohol consumption. Obesity was by far the most important risk factor, estimated to account for 34% of cases. The preventive potential of adult-onset autoimmune diabetes was of similar magnitude as shown for type 2 diabetes in previous studies based on US populations [4,6,7]. Our results suggest that a healthy lifestyle may prevent or delay the development of adult-onset autoimmune diabetes also in individuals with FHD, in line with findings for type 2 diabetes [4,6].

Analysis of individual factors suggest that risk factors of autoimmune diabetes in adults were largely similar to those of type 2 diabetes and include factors known to affect insulin sensitivity such as physical activity [2], BMI [1], and alcohol consumption [3]. These findings fit with data showing that autoimmune diabetes in adults is characterised by insulin resistance in addition to autoimmune destruction of β-cells [8,9]. An important exception is smoking [11]; which was associated with a reduced risk of adult-onset autoimmune diabetes; an effect that may potentially be exerted by inhibition of the autoimmune process. Still, we did not consider smoking as a protective factor in the analyses, due to its many negative effects on other health aspects.

To our knowledge this is the first study investigating the risk of autoimmune diabetes in adults in relation to potential interaction between FHD and lifestyle factors. Our findings suggest additive effects, i.e. the risk is higher in individuals with combined exposure of poor lifestyle and FHD, than in those exposed to only one factor; but no clear interaction as shown previously for type 2 diabetes could be detected [24]. Our analyses were however hampered by small numbers.

The PAR estimations depend on the assumption that the associations we observed reflect causal relationship. For some factors like high BMI, physical activity, and alcohol intake, the support of a biological link are robust; the link between adiposity and insulin resistance is well recognized in several studies [4,7]. Furthermore, physical activity could exert its protective effect through improvement of insulin sensitivity [14]. For moderate alcohol intake the protective effect on type 2 diabetes has been attributed to improvement of insulin sensitivity, reduced postprandial glycemic response, and increasing levels of circulating adiponectin [12]. The influence of psychosocial factors may also be secondary to insulin resistance through a dysfunction of the hypothalamic–pituitary–adrenal axis resulting in excessive cortisol production [25]. The tendency for higher levels of C-peptide in cases with unhealthy lifestyle factors is to be expected if these lifestyle factors primarily are linked to development of insulin resistance. In contrast, cases in the low-risk category tended to have higher GADA levels; this suggests that development of autoimmune diabetes in these adults is linked to autoimmunity rather than insulin resistance. As far as we know, this is the first study estimating PAR related to autoimmune diabetes in adults to date. Undoubtedly there is a need for replications in other populations.

With regard to the generalizability of our findings it should be noted that PAR is dependent both on the strength of the association and the prevalence of specific risk factors in the population. In this context, it is noteworthy that the rate of obesity in Norway is lower (9.0%) than in many other westernized countries like United States (34.3%) and Britain (22.0%) [26]. Thus, the potential for prevention of adult-onset autoimmune diabetes may be different in other countries and this remains to be investigated. Notably, the preventive potential (69%) was within the range of estimates reported for type 2 diabetes in previous studies based on US population [4,6,7].

The major strengths of our study are its large population-based sample, prospective design with long follow-up, fairly high attendance rate. Detailed information on socio-demographic and lifestyle factors, and diabetes incidence were collected and updated during follow-up. Because of limited data on nutritional factors we could not take diet into account. The most likely consequence of this is underestimation of the potential for prevention of adult-onset autoimmune diabetes. Some influence of dietary factors may be exerted through BMI, but there are also dietary factors shown to have a direct effect on the risk on insulin sensitivity, like consumption of whole grain [27]. The influence of dietary factors on adult-onset autoimmune diabetes is an important area for future studies. Self-reported diabetes has shown >95% concurrence with health care records in this population [28], but undiagnosed cases of diabetes will be missed. Ours is the largest prospective study of adult-onset autoimmune diabetes to date as far as we know. Still, the number of cases was insufficient to obtain formal significance levels for stratified analyses. It has been shown that GADA is an autoantibody with the highest penetration and being present in 70-80% of autoimmune diabetes patients [29,30]. The 64% sensitivity and 100% specificity of the GADA assay in the present study makes it unlikely that cases of type 2 diabetes are classified as autoimmune which would seriously bias the results. Reliance on self-reports for most lifestyle factors is not optimal. However, due to the prospective nature of this study, misclassification of lifestyle factors can be assumed to be non-differential, i.e. not differ between cases and non-cases, which will tend to dilute the risk estimates rather than result in overestimations.

Our findings imply that the majority of adult-onset autoimmune diabetes cases might be prevented by healthy lifestyle habits and most importantly maintaining a healthy weight. Such findings are important for public health recommendations. However confirmation from other populations is warranted.

## Acknowledgment

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All authors contributed in writing the manuscript, interpretation of the data and critically reviewed the paper, and read and approved the final manuscript. BR analyses the data and wrote the manuscript under supervision of SC, TA, and VG. KM researched the data. BR is the guarantor of the study. The authors thank the participants in the HUNT Study and also the investigators and the staff of the HUNT data centre for their valuable contribution. An abstract of this work was presented as a poster at the 48th annual meeting of the European Association for the Study of Diabetes, Berlin, Germany, 1-5 October 2012.

## References

1. Eckel RH, Kahn SE, Ferrannini E, Goldfine AB, Nathan DM, et al. (2011) Obesity and type 2 diabetes: what can be unified and what needs to be individualized? J Clin Endocrinol Metab 96: 1654-1663.
2. Hayes C, Kriska A (2008) Role of physical activity in diabetes management and prevention. J Am Diet Assoc 108: S19-23.
3. Carlsson S, Hammar N, Grill V (2005) Alcohol consumption and type 2 diabetes Meta-analysis of epidemiological studies indicates a U-shaped relationship. Diabetologia 48: 1051-1054.
4. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, et al. (2001) Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 345: 790-797.
5. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J (2007) Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 298: 2654-2664.
6. Reis JP, Loria CM, Sorlie PD, Park Y, Hollenbeck A, et al. (2011) Lifestyle factors and risk for new-onset diabetes: a population-based cohort study. Ann Intern Med 155: 292-299.

7. Mozaffarian D, Kamineni A, Carnethon M, Djoussé L, Mukamal KJ, et al. (2009) Lifestyle risk factors and new-onset diabetes mellitus in older adults: the cardiovascular health study. Arch Intern Med 169: 798-807.

8. Naik RG, Brooks-Worrell BM, Palmer JP (2009) Latent autoimmune diabetes in adults. J Clin Endocrinol Metab 94: 4635-4644.

9. Groop L, Tuomi T, Rowley M, Zimmet P, Mackay IR (2006) Latent autoimmune diabetes in adults (LADA)--more than a name. Diabetologia 49: 1996-1998.

10. Hawa MI, Kolb H, Schloot N, Beyan H, Paschou SA, et al. (2013) Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. Diabetes Care 36: 908-913.

11. Rasouli B, Grill V, Midthjell K, Ahlbom A, Andersson T, et al. (2013) Smoking is associated with reduced risk of autoimmune diabetes in adults contrasting with increased risk in overweight men with type 2 diabetes: a 22-year follow-up of the HUNT study. Diabetes Care 36: 604-610.

12. Rasouli B, Ahlbom A, Andersson T, Grill V, Midthjell K, et al. (2013) Alcohol consumption is associated with reduced risk of Type 2 diabetes and autoimmune diabetes in adults: results from the Nord-Trondelag health study. Diabet Med 30: 56-64.

13. Olsson L, Ahlbom A, Grill V, Midthjell K, Carlsson S (2011) High levels of education are associated with an increased risk of latent autoimmune diabetes in adults: results from the Nord-Trøndelag health study. Diabetes Care 34: 102-107.

14. Carlsson S, Midthjell K, Tesfamarian MY, Grill V (2007) Age, overweight and physical inactivity increase the risk of latent autoimmune diabetes in adults: results from the Nord-Trøndelag health study. Diabetologia 50: 55-58.

15. Olsson L, Ahlbom A, Grill V, Midthjell K, Carlsson S (2012) Sleep disturbances and low psychological well-being are associated with an increased risk of autoimmune diabetes in adults. Results from the Nord-Trøndelag Health Study. Diabetes Res Clin Pract 98: 302-311.

16. Krokstad S, Langhammer A, Hveem K, Holmen T, Midthjell K, et al. (2013) Cohort Profile: The HUNT Study, Norway. Int J Epidemiol 42: 968-977.

17. Schlosser M, Mueller PW, Törn C, Bonifacio E, Bingley PJ; Participating Laboratories (2010) Diabetes Antibody Standardization Program: evaluation of assays for insulin autoantibodies. Diabetologia 53: 2611-2620.

18. Davies H, Brophy S, Bain SC, Stephens JW, Lewis J, et al. (2009) GADA testing: the current state of knowledge. Prim Care Diabetes 3: 189-191.

19. Radtke MA, Midthjell K, Nilsen TI, Grill V (2009) Heterogeneity of patients with latent autoimmune diabetes in adults: linkage to autoimmunity is apparent only in those with perceived need for insulin treatment: results from the Nord-Trøndelag Health (HUNT) study. Diabetes Care 32: 245-250.

20. [No authors listed] (2000) Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 894: i-xii, 1-253.

21. (2008) Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation, Geneva.

22. Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlbom A (2005) Calculating measures of biological interaction. Eur J Epidemiol 20: 575-579.

23. Rothman (1998) Modern Epidemiology (2n edn) Lippincott Williams & Wilkins.

24. Hilding A, Eriksson AK, Agardh EE, Grill V, Ahlbom A, et al. (2006) The impact of family history of diabetes and lifestyle factors on abnormal glucose regulation in middle-aged Swedish men and women. Diabetologia 49: 2589-2598.

25. Eriksson AK, Ekbom A, Granath F, Hilding A, Efendic S, et al. (2008) Psychological distress and risk of pre-diabetes and Type 2 diabetes in a prospective study of Swedish middle-aged men and women. Diabet Med 25: 834-842.

26. National obesity observatory (2009) International comparisons of obesity prevalence.

27. Liese AD, Roach AK, Sparks KC, Marquart L, D'Agostino RB Jr, et al. (2003) Whole-grain intake and insulin sensitivity: the Insulin Resistance Atherosclerosis Study. Am J Clin Nutr 78: 965-971.

28. Midthjell K, Holmen J, Bjørndal A, Lund-Larsen G (1992) Is questionnaire information valid in the study of a chronic disease such as diabetes? The Nord-Trøndelag diabetes study. J Epidemiol Community Health 46: 537-542.

29. Sørgjerd EP, Skorpen F, Kvaløy K, Midthjell K, Grill V (2012) Time dynamics of autoantibodies are coupled to phenotypes and add to the heterogeneity of autoimmune diabetes in adults: the HUNT study, Norway. Diabetologia 55: 1310-1318.

30. Sabbah E, Savola K, Kulmala P, Veijola R, Vähäsalo P, et al. (1999) Diabetes-associated autoantibodies in relation to clinical characteristics and natural course in children with newly diagnosed type 1 diabetes. The Childhood Diabetes In Finland Study Group. J Clin Endocrinol Metab 84: 1534-1539.