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DIABETES MELLITUS

The relative importance of modifiable potential risk factors of type 2 diabetes: a meta-analysis of two cohorts

Maarit A. Laaksonen · Paul Knekt · Harri Rissanen · Tommi Härkänen · Esa Virtala · Jukka Marniemi · Arpo Aromaa · Markku Heliövaara · Antti Reunanen

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Abstract Lifestyle factors predict type 2 diabetes occurrence, but their effect in high- and low-risk populations is poorly known. This study determines the prediction of low-risk lifestyle on type 2 diabetes in those with and without metabolic syndrome in a pooled sample of two representative Finnish cohorts, collected in 1978–1980 and 2000–2001. Altogether 8,627 individuals, aged 40–79 years, and free of diabetes and cardiovascular disease at baseline were included in this study. A low-risk lifestyle was defined based on body mass index, exercise, alcohol consumption, smoking, and serum vitamin D concentration. The metabolic syndrome was defined according to the International Diabetes Federation including obesity, blood pressure, serum HDL cholesterol, serum triglycerides, and fasting glucose. During a 10-year follow-up, altogether 226 type 2 diabetes cases occurred. Overweight was the strongest predictor of type 2 diabetes (population attributable fraction (PAF) = 77%, 95% confidence interval (CI): 53, 88%). Together with lack of exercise, unsatisfactory alcohol consumption, smoking, and low vitamin D concentration it explained 82% of the cases. Altogether 62% (CI: 47, 73%) of the cases were attributable to the metabolic syndrome and 92% (CI: 67, 98%) to the most unfavourable combination of its components. The metabolic syndrome did not modify the prediction of lifestyle factors but persons with normal blood pressure benefited more from positive changes in exercise, alcohol consumption, and smoking than those with elevated blood pressure (P for interaction = 0.01). In conclusion, modification of lifestyle factors apparently reduces type 2 diabetes risk, especially in persons with normal blood pressure.

Keywords Type 2 diabetes · Low-risk lifestyle · Metabolic syndrome · Cohort studies · Pooling · Population attributable fraction (PAF)

Abbreviations

BMI	Body mass index
CI	95% Confidence interval
HDL	High-density lipoprotein
Health 2000	Health 2000 Survey
IDF	International Diabetes Federation
MFH	Mini-Finland Health Survey
PAF	Population attributable fraction
RR	Relative risk
WHO	World Health Organisation

Introduction

The occurrence of type 2 diabetes is, mainly due to the ongoing obesity epidemic, continuously growing worldwide [1]. Besides obesity, other lifestyle factors, such as exercise, smoking, alcohol consumption, and some dietary habits [2], and combinations of these [3–5] have also been shown to predict the occurrence of this disease. Recently it has been suggested that low serum vitamin D concentration, related to lifestyle both through the diet (e.g. fish consumption) and outdoor activity (sunlight), may also predict type 2 diabetes occurrence [6, 7].

M. A. Laaksonen · P. Knekt (✉) · H. Rissanen · T. Härkänen · E. Virtala · A. Aromaa · M. Heliövaara · A. Reunanen
National Institute for Health and Welfare, PL 30, 00271 Helsinki, Finland
e-mail: paul.knekt@thl.fi

J. Marniemi
National Institute for Health and Welfare, Peltolantie 3, 20720 Turku, Finland

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Definitions of metabolic syndrome help to identify individuals at high risk for type 2 diabetes, the one provided by the International Diabetes Federation (IDF) being the most recent [8]. Although the prediction of individual factors in this definition (i.e. waist circumference, blood pressure, serum HDL cholesterol, serum triglycerides and fasting glucose) is well known [9–11], the risk attributable to the syndrome as a whole in a representative population sample has not been well described [9, 12, 13]. In addition, a variety of risk scores combining factors related to lifestyle and metabolic syndrome have been proposed for identifying high-risk individuals [11, 14–18].

It has been suggested that the role of lifestyle modification in reducing type 2 diabetes incidence is especially important in persons at high risk [4, 19]. Many intervention studies have also shown that positive changes in lifestyle, i.e. weight loss, increased exercise and improved diet, reduce the incidence of type 2 diabetes in high-risk individuals [20, 21]. However, the prediction of the modifiable lifestyle factors on diabetes incidence in individuals with and without metabolic syndrome has not yet been compared [22], and it is thus not known whether the effect of lifestyle modifications actually differs in high- and low-risk individuals.

This study explores the relative importance of modifiable lifestyle factors and components of the metabolic syndrome on type 2 diabetes by presenting population attributable fraction (PAF) estimates for them, and compares the expected importance of the lifestyle modification in persons with and without metabolic syndrome in a pooled sample of two representative Finnish cohorts.

Methods

Study populations

The present study is based on two cohorts, the Mini-Finland Health Survey (MFH) carried out in 1978–1980 [23] and the Health 2000 Survey (Health 2000) carried out in 2000–2001 [24]. Both samples were stratified two-stage cluster samples, representative of the Finnish adult population aged 30 years and over [25]. The MFH sample comprised 8,000 individuals from 40 geographical areas, and the Health 2000 sample 8,028 individuals from 80 areas. A total of 7,217 subjects (90% of the sample) in MFH and 6,771 subjects (84% of the sample) in Health 2000 participated in a health examination. Persons aged 40–79 years and free of type 2 diabetes and cardiovascular diseases at baseline were included. The final data comprised a total of 4,517 individuals (2,004 men and 2,513 women) from the MFH and 4,110 individuals (1,850 men and 2,260 women) from Health 2000.

Risk assessment

Variables considered

Data on education, smoking, leisure time exercise, alcohol consumption, previous diseases (e.g. type 2 diabetes and cardiovascular diseases), and antihypertensive medication were self-reported in a health interview or a self-administered questionnaire at baseline. Height and weight were measured at a health examination, and body mass index (BMI) was calculated. Waist circumference was measured in Health 2000 only. Casual blood pressure was measured twice with a 1.5 minute interval by the auscultatory method, and fasting blood samples were taken and stored at −20°C (MFH) or −70°C (Health 2000). Serum HDL cholesterol, serum triglycerides, and fasting glucose levels were determined as soon as technically possible (usually some weeks) after the samples were taken. Serum HDL cholesterol was analysed using Mg-dextrane sulphate precipitation in MFH [26] and using a direct method in Health 2000 (HDL-C Plus, Roche Diagnostics, Germany). Serum triglyceride concentration was determined fully enzymatically (MFH: Boehringer, Mannheim, Germany; Health 2000: Olympus System Reagent, Germany). Plasma samples were used for glucose analysis in MFH (glucose oxidase, Boehringer, Mannheim, Germany) and serum samples in Health 2000 (hexokinase, Olympus System Reagent, Germany). Serum 25-hydroxyvitamin D concentrations were determined in 2001–2004 using radioimmunoassay (RIA, DiaSorin, Minnesota). Every variable was standardised between the two cohorts to the extent possible, and an indicator variable for missing categories was created for each variable.

Low-risk lifestyle

Five modifiable lifestyle factors were used to define low-risk lifestyle level, i.e. BMI, exercise, smoking, alcohol consumption, and serum vitamin D. Low risk was defined as a BMI <25.0 kg/m^2, occasional or regular exercise (approximately 30 minutes or more per day), not smoking, alcohol consumption 1–99 g/week in women and 1–199 g/week in men, and serum vitamin D level above the median (>39 nmol/l in MFH and >44 nmol/l in Health 2000).

The metabolic syndrome

The metabolic syndrome was, according to the International Diabetes Federation (IDF) [8], defined as waist circumference $\geq$94 cm in men and $\geq$80 cm in women together with an unsatisfactory value in at least two of the following variables: blood pressure, serum HDL cholesterol, serum triglycerides, and fasting glucose. Blood pressure was

considered unsatisfactory if the mean level of two systolic blood pressure measurements was ≥130 mmHg or the mean level of two diastolic blood pressure measurements was ≥85 mmHg or antihypertensive medication was used. Unsatisfactory serum HDL cholesterol included serum values ≤1.02 mmol/l in men and ≤1.29 mmol/l in women. Serum triglycerides were considered unsatisfactory if the serum value was ≥1.7 mmol/l and fasting glucose was considered unsatisfactory if it was ≥5.6 mmol/l. Since waist circumference was not measured in MFH, BMI ≥25 kg/m^2 was used as its proxy measure in definition of metabolic syndrome (IDF criteria). The relative risk (95% CI) of diabetes for individuals with metabolic syndrome according to the original definition and the proxy definition in Health 2000 were 6.70 (3.61, 12.4) and 6.78 (3.72, 12.4), respectively. The corresponding PAF values were 0.71 (0.52, 0.83) and 0.71 (0.52, 0.82).

Diabetes incidence

A cohort study design with type 2 diabetes incidence as the outcome was adopted. The incident diabetes cases were identified based on diabetes medication received. Under the Sickness Insurance Act, all diabetics needing drug therapy are entitled to reimbursement of drug costs, eligibility for which requires a detailed medical certificate from an attending physician [27]. A central register of all patients receiving drug reimbursement is kept by the Social Insurance Institution. Participants of the present study were linked to this register by the unique code assigned to each Finnish citizen. All medical certificates of these cases were checked to meet the WHO diagnostic criteria for type 2 diabetes mellitus [28]. In addition, disease events leading to hospitalisation were identified by linking data from the Finnish Hospital Discharge Register [29]. Furthermore, information on mortality was based on death certificates obtained from Statistics Finland [30], and the individuals with type 2 diabetes cited as the principal cause of death were classified as diabetes cases.

The follow-up time was defined as days from the baseline examination to the date of type 2 diabetes occurrence, death, or end of follow-up, whichever came first. The follow-up time was 10 years in MFH and 7 years in Health 2000. During the follow-ups, a total of 145 individuals (67 men and 78 women) in MFH and 81 (42 men and 39 women) in Health 2000 developed type 2 diabetes.

Statistical methods

The cohort-specific analyses

Cox's model [31] was used to assess the relative risk (RR) and a piecewise constant hazards model [32] to assess the population attributable fraction (PAF) for the potential risk factors of type 2 diabetes incidence. The PAF estimates the proportion of cases (A) in a given population that would theoretically not have occurred if all the individuals had had low-risk target values of the risk factors of interest (X^*) instead of their true values (X): $\mathrm{PAF} = [P(A|X) - P(A|X^*)]/P(A|X) = 1 - P(A|X^*)/P(A|X)$, where $P(A|X)$ is the probability of outcome occurrence given the risk factors X [33]. This is done by combining information about the prevalence of the risk factor in the population with estimates of the strength of the association between the risk factor and the outcome. The risk factors X are assumed to include modifiable and non-modifiable risk factors and confounding factors, and thus only the modifiable risk factors whose effect we are interested in measuring change their value in X^* while the rest of the factors retain their values. In the calculation of PAF, a causal relation between the risk factors and the outcome is assumed. Since the outcome of interest is type 2 diabetes and the risk factors for this disease may also be related to mortality, censoring due to death was also taken into account in the calculation of PAF [34]. Two-sided 95% confidence intervals of PAF were estimated using the delta method. To avoid assumptions about the shape of the relationship between the potential continuous risk factors and type 2 diabetes incidence in the statistical analyses, RR:s and PAF:s were estimated for categories of these variables.

Two main effects models were defined. The first model (both RR and PAF) included age, sex, and separately each of the five lifestyle factors (i.e. BMI, physical exercise, smoking, alcohol consumption, and serum vitamin D), or each of the components of the metabolic syndrome (i.e. BMI, blood pressure, serum HDL cholesterol, serum triglycerides, and fasting glucose), or the metabolic syndrome as a whole. The second model (only PAF) included age, sex, and combinations of lifestyle factors or components of metabolic syndrome adjusted for the factors not included in the combination.

Possible modification by sex, age, metabolic syndrome or its components on the prediction of the lifestyle factors on type 2 diabetes risk was studied by including an interaction term between the risk factor or risk factor combination of interest and the potential effect modifying factor in the model. The statistical significance of effect modification was studied by calculating the 95% confidence interval of the difference of the PAF estimates between the categories of the effect modifying factor using the delta method.

Pooling

The pooling methodology is described in more detail elsewhere [35] and is only briefly summarized here. The

sub-cohort specific logs of RRs or complementary-log transformed PAFs or untransformed PAF differences were combined, weighting them by the inverse of their variance, in a random-effects model [36]. Heterogeneity among the study-specific RRs or PAFs was tested using the asymptotic DerSimonian and Laird Q statistic [36]. The potential heterogeneity due to sex was tested by the Wald test [37].

The calculations were performed using PROC PHREG, PROC TPHREG, PROC LIFEREG, PROC MIXED and PROC IML of SAS (version 9.1; SAS Institute, Cary, NC).

Results

Description of the study populations

During the 20-year period between the MFH and Health 2000 the educational level in Finland rose and the proportion of persons occasionally or regularly exercising increased (Table 1). Of the components of the metabolic syndrome, both blood pressure and serum HDL cholesterol improved. At the same time, however, the Finnish population became more obese and heavy use of alcohol increased. The relative risk of diabetes during a 10-year follow-up from baseline did not differ between the two samples with the exception of fasting glucose level (P for heterogeneity <0.001).

PAF for lifestyle factors and components of metabolic syndrome

Obesity appeared to predict well type 2 diabetes occurrence: 77% (CI: 53, 88%) of all cases could have been avoided if everyone's BMI had been under 25.0 kg/m^2 (Table 2). Of the other lifestyle factors considered, only smoking predicted independently type 2 diabetes occurrence (PAF = 10%, CI: 2, 17%). A combination of these variables, however, improved the prediction; altogether 82% (CI: 70, 90%) of the diabetes cases could have been prevented if all individuals had belonged to the low-risk category with respect to all lifestyle factors and 27% (CI: 11, 40%) if they had belonged to the low-risk category in all other variables but BMI.

All 5 components of the metabolic syndrome appeared to predict diabetes incidence, showing sex- and age-adjusted PAF values varying from 24 to 76% (Table 3). The PAF for metabolic syndrome was 62% (CI: 47, 73%). When all its five components were modified to low-risk level, the PAF was, however, much higher, 92% (CI: 67, 98%). Also the PAF for modification to the low-risk category in four other variables except BMI was considerable (PAF = 77%, CI: 36, 91%).

Effect modification by metabolic syndrome and socio-demographic factors

The metabolic syndrome as a whole or its most important component, obesity, did not statistically significantly modify the prediction of lifestyle factors (i.e. exercise, alcohol consumption, smoking, and serum vitamin D level) on type 2 diabetes incidence (Table 4). A simultaneous low-risk level in exercise, alcohol consumption and smoking did, however, have a statistically significantly better prediction in persons with normal blood pressure (PAF = 58%, CI: 16, 79%) in comparison to those with elevated blood pressure (PAF = 15%, CI: 3, 26%) (P for interaction = 0.01). On the other hand, in MFH, more type 2 diabetes cases could have been avoided by modifying BMI to the low-risk category among those with (PAF = 77%, CI: 60, 87%) than without (PAF = 10%, CI: −66, 52%) elevated blood pressure (P for interaction = 0.02). In Health 2000, the respective estimates could not be obtained due to too few low-BMI non-hypertensive diabetes cases, but the pooled results obtained using a higher cut-off value of 28 for BMI indicated a similar, statistically significant, result (data not shown).

Study of the interactions between lifestyle and socio-demographic factors (i.e. sex and age) showed that belonging to the low-risk category for smoking had a stronger prediction on reduction of type 2 diabetes in younger persons (P for interaction = 0.002) and having a higher serum vitamin D a stronger prediction in women (P for interaction = 0.02).

Discussion

Over 80% of all incident diabetes cases occurring in these two samples representing the Finnish population, could be attributed to failure to follow a low-risk lifestyle, including a body mass index under 25, adequate exercise, moderate alcohol consumption, non-smoking, and a satisfactory vitamin D level. This study thus suggests that the majority of type 2 diabetes cases could be avoided by modifications of lifestyle, which is in line with previous findings [3–5].

Obesity was the most important predictor of type 2 diabetes. Accordingly, and in line with previous cohort [3–5] and intervention [21, 38] studies, weight control would apparently be the most important strategy in type 2 diabetes prevention. The four other lifestyle variables were also significantly associated with an increased risk of diabetes, in agreement with previous studies [3, 5]. At the population level, however, only one-fourth of the incident disease cases seemed attributable to these four variables collectively, smoking being the only single variable significantly associated with reduced diabetes risk.

Table 1 Age- and sex-adjusted relative risks (RR) and their 95% confidence intervals (CI) of type 2 diabetes between categories of socio-demographic factors, lifestyle factors, and components of the metabolic syndrome

Variable	MFH					Health 2000					Pooled		P^a
	n	*N*	%	RR	95% CI	*n*	*N*	%	RR	95% CI	RR	95% CI	
Socio-demographic factors													
Sex													
Male	67	2,004	44.4	1		42	1,850	45.0	1		1		
Female	78	2,513	55.6	0.78	0.56, 1.09	39	2,260	55.0	0.70	0.45, 1.09	0.75	0.58, 0.98*	0.71
Age (years)[b]													
40–49	28	1,576	34.9	1		20	1,528	37.2	1		1		
50–59	47	1,431	31.7	1.95	1.22, 3.11*	31	1,301	31.6[c]	1.83	1.04, 3.21*	1.90	1.32, 2.72*	0.87
60–69	49	952	21.1	3.37	2.11, 5.37*	16	813	19.8	1.58	0.82, 3.04	2.39	1.14, 5.02*	0.06
70–79	21	558	12.3[c]	2.99	1.69, 5.30*	14	468	11.4	2.61	1.31, 5.18*	2.83	1.83, 4.39*	0.76
Education													
Basic	116	3,337	74.1	1		34	1,545	37.7	1		1		
Intermediate	23	962	21.4	0.75	0.48, 1.18	33	1,491	36.4	1.18	0.71, 1.95	0.92	0.60, 1.44	0.19
High	4	205	4.5[c]	0.62	0.23, 1.68	14	1,059	25.9	0.74	0.39, 1.42	0.70	0.41, 1.21	0.77
Modifiable lifestyle factors													
Body mass index (kg/m^2)[d]													
<25	16	1,809	40.1	1		4	1,404	34.3[c]	1		1		
≥25	129	2,705	59.9	5.09	3.03, 8.56*	77	2,695	65.7[c]	9.36	3.42, 25.6*	5.89	3.54, 9.80*	0.29
Exercise													
No	65	1,646	36.5	1		26	970	24.1	1		1		
Occasional or regular	80	2,864	63.5	0.72	0.52, 1.01	54	3,051	75.9	0.65	0.40, 1.03	0.69	0.53, 0.91*	0.78
Alcohol consumption[e]													
None	88	2,238	49.6	1		33	1,208	30.0	1		1		
Moderate	45	1,953	43.3	0.61	0.41, 0.90*	30	2,187	54.3	0.52	0.31, 0.86*	0.57	0.42, 0.78*	0.63
Heavy	12	321	7.1	1.01	0.53, 1.94	17	633	15.7	1.05	0.56, 1.99	1.03	0.66, 1.63	0.94
Smoking													
Never smoked	77	2,598	57.6	1		35	2,135	52.3	1		1		
Former smoker	35	942	20.9	1.38	0.87, 2.20	24	954	23.4	1.56	0.90, 2.69	1.45	1.02, 2.07*	0.75
Current smoker													
Pipe or cigar only or <30 cigarettes/day	27	893	19.8	1.30	0.80, 2.11	16	899	22.1[c]	1.29	0.69, 2.39	1.29	0.88, 1.90	0.99
≥30 cigarettes/day	6	79	1.7[c]	3.88	1.59, 9.49*	6	91	2.2	4.87	1.95, 12.2*	4.34	2.29, 8.22*	0.73
Serum vitamin D median (nmol/l)[f]													
≤median	86	2,169	49.0	1		42	1,939	50.2	1		1		
>median	56	2,257	51.0	0.63	0.45, 0.89*	32	1,920	49.8	0.73	0.46, 1.15	0.66	0.50, 0.87*	0.63
Metabolic syndrome and its components													
Waist circumference[g]													
Normal						2	1,150	28.2	1				
Large						79	2,932	71.8	15.2	3.74, 62.2*			
Blood pressure[h]													
Normal	10	653	14.5	1		9	1,270	31.0	1		1		
Elevated	135	3,262	85.5	1.93	1.00, 3.69*	72	2,827	69.0	3.20	1.57, 6.50*	2.43	1.48, 3.99*	0.30
Serum triglycerides (mmol/l)[i]													
<1.7	49	3,177	70.4	1		27	2,750	67.2[c]	1		1		
≥1.7	96	1,338	29.6	4.46	3.15, 6.31*	53	1,339	32.8[c]	3.90	2.44, 6.23*	4.25	3.21, 5.62*	0.65
Serum HDL cholesterol (mmol/l)[j]													
Low	24	281	93.8	1		47	1,355	66.9	1		1		
High	121	4,233	6.2	0.33	0.21, 0.51*	33	2,734	33.1	0.34	0.22, 0.53*	0.33	0.24, 0.46*	0.92

Table 1 continued

Variable	MFH					Health 2000					Pooled		P^a
	n	*N*	%	RR	95% CI	*n*	*N*	%	RR	95% CI	RR	95% CI	
Serum fasting glucose (mmol/l)[k]													
<5.6	81	3,350	74.2	1		17	2,654	64.9	1		1		
≥5.6	64	1,165	25.8	2.15	1.55, 3.00*	63	1,435	35.1	6.70	3.88, 11.6*	3.72 [1]	1.22, 11.3*	<0.001
IDF proxy[m]													
Negative	41	3,094	68.6	1		13	2,379	58.1	1		1		
Positive	104	1,419	31.4	5.22	3.62, 7.52*	67	1,715	41.9	6.78	3.72, 12.4*	5.60	4.10, 7.65*	0.47

HDL = high-density lipoprotein, Health 2000 = Health 2000 Survey, MFH = Mini-Finland Health Survey, *n* = Number of disease cases in respective category, *N* = Number of subjects in respective category

[a] *P* value for heterogeneity between pooled samples

[b] Mean (SD) age in MFH 55.3 (10.4) years and in Health 2000 54.7 (10.2) years

[c] Per cents rounded to sum up to 100

[d] Mean (SD) value of body mass index in MFH 26.4 (3.98) kg/m^2 and in Health 2000 27.2 (4.56) kg/m^2

[e] Moderate: 1–99 g/week for women and 1–199 g/week for men. Heavy: ≥100 g/week for women and ≥200 g/week for men

[f] Evaluated separately in MFH (39 nmol/l) and in Health 2000 (44 nmol/l)

[g] Normal: <80 for women and <94 for men. Large: ≥80 for women and ≥94 for men

[h] Elevated: SBP ≥130 mmHg or DBP ≥85 mmHg or antihypertensive medication. Normal: Not elevated

[i] Mean (SD) value of serum triglycerides in MFH 1.54 (0.85) mmol/l and in Health 2000 1.59 (1.02) mmol/l

[j] Low: ≤1.29 mmol/l in women and ≤1.02 mmol/l in men. High: >1.29 mmol/l in women and >1.02 mmol/l in men

[k] Mean (SD) value of serum fasting glucose in MFH 5.27 (0.59) mmol/l and in Health 2000 5.45 (0.75) mmol/l

[l] Statistically significant interaction with sex ($P = 0.003$): MFH: RR 2.10 (95% CI: 1.30, 3.41) for men and 2.19 (95% CI: 1.39, 3.45) for women. Health 2000: RR 12.3 (95% CI: 4.37, 34.5) for men and 4.86 (95% CI: 2.44, 9.66) for women

[m] Waist circumference in the International Diabetes Federation (IDF) definition of the metabolic syndrome was replaced by a proxy measure BMI in which the category normal[f] is replaced by BMI <25 kg/m^2 and the category large by BMI ≥25 kg/m^2

* Statistically significant association (*P* value < 0.05)

In the present study, two-thirds of the disease cases could be attributed to having metabolic syndrome. This finding is in agreement with the fact that the metabolic syndrome is a strong predictor of type 2 diabetes [9, 13]. In accordance with previous cohort [9, 10] and intervention [21, 38] studies, all 5 single components of the metabolic syndrome (i.e. waist circumference/BMI, blood pressure, serum HDL cholesterol, serum triglycerides, and fasting glucose) also predicted type 2 diabetes occurrence in our study. In fact we found that over 90% of all cases could have been avoided if all individuals had belonged to the low-risk category in all five components and two-thirds if they had belonged to the low-risk category in the four components less emphasised in the definition of the metabolic syndrome.

Of special importance is the question of whether the metabolic syndrome modifies possible effects of changes in lifestyle. As far as we know, this is the first study to explore the potential effect modification of metabolic syndrome on prediction of lifestyle modifications on type 2 diabetes incidence. The present study did not find any interactions between lifestyle and metabolic syndrome as defined according to the International Diabetes Federation (IDF). It appeared, however, that positive changes in smoking, alcohol consumption and exercise habits could have prevented more type 2 diabetes cases among persons with normal blood pressure than among persons with elevated blood pressure. Our results thus contradict the frequent claim that lifestyle modifications have greater effect in high-risk individuals [19]. Reduction of BMI, on the other hand, was more strongly associated to reduced diabetes risk in persons with than without elevated blood pressure. This result is consistent with a finding according to which weight reduction had a stronger effect on type 2 diabetes incidence in high-risk individuals than in low-risk individuals [39, 40]. Overall, lifestyle factors not involved in the metabolic syndrome seem to play a more important role in the prevention of type 2 diabetes in low-risk individuals. Therefore, as regards the constantly growing diabetes epidemic, it is important to target lifestyle-related prevention not only to those at high risk of developing type 2 diabetes, but also at the entire population [41].

Several methodological issues need to be considered when interpreting these findings. Considerable advantages

Table 2 Population attributable fractions (PAF) and their 95% confidence intervals (CI) for modifiable lifestyle factors of type 2 diabetes

Variable[a]	MFH		Health 2000		Pooled		P^b
	PAF	95% CI	PAF	95% CI	PAF	95% CI	
Model 1[c]							
A. Body mass index	0.71	0.55, 0.82*	0.84	0.59, 0.94*	0.75	0.59, 0.85*	0.27
B. Exercise	0.11	−0.03, 0.23	0.10	−0.04, 0.23	0.11	0.01, 0.19*	0.95
C. Alcohol consumption[d]	0.03	−0.02, 0.08	0.10	−0.01, 0.20	0.05	−0.01, 0.11	0.25
D. Smoking[e]	0.05	−0.04, 0.14	0.08	−0.06, 0.20	0.06	−0.02, 0.13	0.73
E. Serum vitamin D	0.21	0.03, 0.35*	0.14	−0.11, 0.34	0.18	0.04, 0.30*	0.64
Model 2[f]							
A. Body mass index	0.71	0.54, 0.81*	0.87	0.59, 0.96*	0.77	0.53, 0.88*	0.20
B. Exercise	0.03	−0.11, 0.16	0.07	−0.09, 0.20	0.05	−0.06, 0.14	0.76
C. Alcohol consumption[d]	0.02	−0.03, 0.07	0.08	−0.05, 0.19	0.03	−0.02, 0.07	0.42
D. Smoking[e]	0.10	0.01, 0.18*	0.10	−0.05, 0.23	0.10	0.02, 0.17*	0.98
E. Serum vitamin D	0.17	−0.02, 0.32	0.01	−0.28, 0.23	0.11	−0.06, 0.25	0.30
B, C, D	0.15	−0.01, 0.28	0.21	0.02, 0.37*	0.17	0.05, 0.28*	0.59
B, C, D, E	0.30	0.03, 0.45*	0.22	−0.06, 0.43	0.27	0.11, 0.40*	0.63
A, B, C, D, E	0.80	0.65, 0.88*	0.90	0.67, 0.97*	0.82	0.70, 0.90*	0.30

MFH = Mini-Finland Health Survey, Health 2000 = Health 2000 Survey

[a] Variables in this table correspond to the variables and their classification in Table 1. Population attributable fraction estimates the reduction in type 2 diabetes if all persons belonged to the category with the lowest type 2 diabetes risk, if not otherwise mentioned

[b] P for heterogeneity between pooled samples

[c] Variable mentioned, adjusted for age and sex

[d] The category with the lowest type 2 diabetes risk, i.e. moderate alcohol consumption, is used as the reference category, but the type 2 diabetes risk of non-users remains unchanged

[e] The category with the lowest type 2 diabetes risk, i.e. have never smoked, is used as the reference category, but the type 2 diabetes risk of former smokers remains unchanged

[f] Variable/s mentioned, adjusted for age, sex and other lifestyle factors

* Statistically significant association ($P < 0.05$)

of this study are the relatively large amount of data based on two independent representative samples of the whole Finnish population, including both men and women, and the cohort study design. Also, the use of population attributable fraction designed for cohort studies with a single disease as the outcome, taking into account censoring due to death, is a definite advantage as it enables an accurate analysis of the population-level importance of the risk factors. Furthermore, the PAF estimates were pooled for the first time in this study, increasing the power to detect associations. The fact that practically all known important lifestyle variables and all components of the metabolic syndrome used in its different definitions were included further provided the opportunity for a multifaceted investigation of the interplay within and between lifestyle and the metabolic syndrome. The only factors missing were waist circumference as a part of the metabolic syndrome (IDF definition) and dietary habits as a part of lifestyle, neither of which were available in the MFH data. Waist circumference was replaced by body mass index and, as stated in the methodology section, this proxy IDF definition of the metabolic syndrome gave results that were practically identical to those of the original IDF definition in the Health 2000 population. Dietary habits were replaced by serum vitamin D level, apparently correlating with both healthy dietary intake and healthy lifestyle, as its main sources in this Finnish low vitamin D population were fish consumption and exposure to the sun. It has also currently been shown that vitamin D is an important determinant of type 2 diabetes incidence, possibly due to its influence on the pathogenesis of the disease [6, 7].

There are also several factors related to the assumptions, estimation and pooling of PAF that should be considered. First, all lifestyle factors included in this study have not definitely been stated causal. Because these factors are known to be very strong determinants of diabetes occurrence, the assumption of a causal connection is, however, realistic. In addition, in the estimation of PAF, according to its traditional definition, an immediate reduction in disease

Table 3 Population attributable fractions (PAF) and their 95% confidence intervals (CI) for components of metabolic syndrome

Variable[a]	MFH		Health 2000		Pooled		P^b
	PAF	95% CI	PAF	95% CI	PAF	95% CI	
Model 1[c]							
A. Body mass index	0.71	0.55, 0.82*	0.84	0.59, 0.94*	0.75	0.59, 0.85*	0.27
B. Blood pressure	0.41	−0.08, 0.68	0.60	0.26, 0.78*	0.51	0.25, 0.68*	0.37
C. Serum triglycerides	0.51	0.38, 0.60*	0.48	0.30, 0.62*	0.50	0.40, 0.58*	0.80
D. Serum HDL cholesterol	0.11	0.04, 0.17*	0.38	0.20, 0.52*	0.24	−0.08, 0.47	0.006
E. Fasting glucose	0.23	0.11, 0.33*	0.65	0.48, 0.77*	0.47	−0.16, 0.76	<0.001
Metabolic syndrome[d]	0.57	0.45, 0.67*	0.71	0.52, 0.82*	0.62	0.47, 0.73*	0.19
Model 2[e]							
A. Body mass index	0.63	0.41, 0.76*	0.76	0.38, 0.91*	0.66	0.48, 0.77*	0.42
B. Blood pressure	0.13	−0.57, 0.52	0.33	−0.21, 0.64	0.24	−0.16, 0.50	0.53
C. Serum triglycerides	0.44	0.30, 0.55*	0.34	0.10, 0.51*	0.40	0.29, 0.50*	0.38
D. Serum HDL cholesterol	0.05	−0.01, 0.12	0.22	−0.01, 0.40	0.11	−0.06, 0.25	0.15
E. Fasting glucose	0.19	0.06, 0.29	0.62	0.43, 0.75*	0.43	−0.20, 0.73	0.001
B, C, D, E	0.62	0.28, 0.80*	0.86	0.71, 0.94*	0.77	0.36, 0.91*	0.04
A, B, C, D, E	0.85	0.68, 0.93*	0.96	0.89, 0.99*	0.92	0.67, 0.98*	0.04

MFH = Mini-Finland Health Survey, Health 2000 = Health 2000 Survey, HDL = high-density lipoprotein

[a] Variables in this table correspond to the variables and their classification in Table 1. Population attributable fraction estimates the reduction in type 2 diabetes if all persons belonged to the category with the lowest type 2 diabetes risk, if not otherwise mentioned

[b] P for heterogeneity between pooled samples

[c] Variable mentioned, adjusted for age and sex

[d] Waist circumference in the International Diabetes Federation (IDF) definition of the metabolic syndrome was replaced by a proxy measure BMI in which the category normal (<80 cm for women and <94 cm for men) was replaced by BMI <25 kg/m^2 and the category large (≥80 cm for women and ≥94 cm for men) by BMI ≥25 kg/m^2

[e] Variable/s mentioned, adjusted for age, sex and other components of the metabolic syndrome

* Statistically significant association ($P < 0.05$)

risk after the modification of the risk factors was hypothesised, even though in real life there tends to be a certain delay before the reduction in disease risk is seen. Second, some factors may have caused underestimation of the strength of association and, accordingly, led to conservative PAF estimates: some of the variables, especially exercise, apparently include measurement errors. Also, possible changes may have appeared in the lifestyle variables during follow-up. Because the follow-up was at most 10 years, such changes are likely to have been fairly small, however. Despite the large number of variables considered in this study, the possibility of residual confounding cannot be fully excluded either. Also, since incident diabetes cases were identified based on diabetes medication received, patients receiving dietary treatment and individuals with undiagnosed diabetes were included among non-cases, leading to conservative estimates. By contrast, multiple comparisons may have led to some spurious positive findings. Third, as the associations between diabetes occurrence and its determinants were mainly consistent in the two samples studied, the pooling of these samples was justified. The only deviations from this rule were found for fasting glucose and for serum HDL cholesterol, which were stronger predictors in Health 2000, possibly due to the different composition of the reference category or a higher prevalence of unsatisfactory values. Fasting glucose was also the only variable significantly associated with sex. This heterogeneity both within and between the samples resulted in a wider confidence interval for the pooled estimate.

In conclusion, this study provides further evidence that weight control is the primary diabetes prevention method and that adequate exercise, moderate alcohol consumption, non-smoking, and a satisfactory vitamin D level also play an important role. Metabolic syndrome does not modify the prediction of lifestyle factors. Of its single components blood pressure, however, modifies prediction so that individuals with elevated blood pressure apparently benefit less from positive changes in exercise, smoking, or alcohol consumption. Further large cohort studies on the prediction of lifestyle factors in total population covering both high-

Table 4 Population attributable fractions (PAF) and their 95% confidence intervals (CI) for modifiable lifestyle factors of type 2 diabetes by categories of potential effect modifying factors and *P*-values for their differences in a pooled sample of Mini-Finland Health Survey (MFH) and Health 2000 Survey

Variable[a,b]	Effect modifying factor				*P* for interaction
	Category A		Category B		
	PAF_A	95% CI	PAF_B	95% CI	
	Metabolic syndrome				
	A = No		B = Yes		
B. Exercise	−0.01	−0.19, 0.15	0.08	−0.04, 0.18	0.44
C. Alcohol consumption[c]	−0.02	−0.15, 0.10	0.06	−0.04, 0.16	0.39
D. Smoking[d]	0.09	−0.08, 0.24	0.07	−0.01, 0.15	0.78
E. Serum vitamin D	0.04	−0.26, 0.27	0.16	−0.02, 0.30	0.35
B, C, D	0.20	0.03, 0.34*	0.06	−0.19, 0.27	0.77
B, C, D, E[e]	0.13	−0.31, 0.43	0.29	0.03, 0.48*	0.47
	Sex				
	A = Men		B = Women		
A. Body mass index	0.77	0.57, 0.88*	0.79	0.11, 0.95*	0.74
B. Exercise	0.07	−0.06, 0.19	0.12	−0.03, 0.24	0.70
C. Alcohol consumption[c]	0.09	−0.00, 0.17	0.01	−0.06, 0.08	0.08
D. Smoking[d]	0.12	−0.03, 0.24	0.04	−0.04, 0.11	0.33
E. Serum vitamin D	0.04	−0.15, 0.20	0.33	0.12, 0.50*	0.02
B, C, D	0.22	0.04, 0.36*	0.17	0.01, 0.30*	0.61
B, C, D, E	0.22	−0.02, 0.40	0.38	0.15, 0.55*	0.32
A, B, C, D, E	0.83	0.65, 0.92*	0.83	0.63, 0.92*	0.80
	Age				
	A = 40–59 years		B = 60–79 years		
A. Body mass index	0.77	0.48, 0.90*	0.73	0.49, 0.85*	0.74
B. Exercise	0.13	−0.00, 0.24	0.07	−0.09, 0.20	0.57
C. Alcohol consumption[c]	0.06	−0.04, 0.15	0.02	−0.02, 0.06	0.43
D. Smoking[d]	0.16	0.04, 0.27*	−0.04	−0.12, 0.03	0.002
E. Serum vitamin D	0.11	−0.08, 0.26	0.29	0.06, 0.46*	0.15
B, C, D	0.27	0.12, 0.40*	0.06	−0.12, 0.22	0.06
B, C, D, E	0.32	0.12, 0.47*	0.25	−0.03, 0.46	0.71
A, B, C, D, E	0.87	0.50, 0.97*	0.79	0.57, 0.90*	0.67

[a] Adjusted for sex and age

[b] Variables in this table correspond to the variables and their classification in Table 1. Population attributable fraction estimates the reduction in type 2 diabetes if all persons belonged to the category with the lowest type 2 diabetes risk, if not mentioned otherwise

[c] The category with the lowest type 2 diabetes risk, i.e. moderate alcohol consumption, is used as the reference category, but the type 2 diabetes risk of non-users remains unchanged

[d] The category with the lowest type 2 diabetes risk, i.e. have never smoked, is used as the reference category, but the type 2 diabetes risk of former smokers remains unchanged

[e] Pooled effect modification analysis could not be carried out due to too few diabetes cases in some low-risk strata of Health 2000 data, and therefore these figures derive from MFH data only

* Statistically significant association (*P* value < 0.05)

and low-risk individuals are, however, needed to verify these findings.

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