2017

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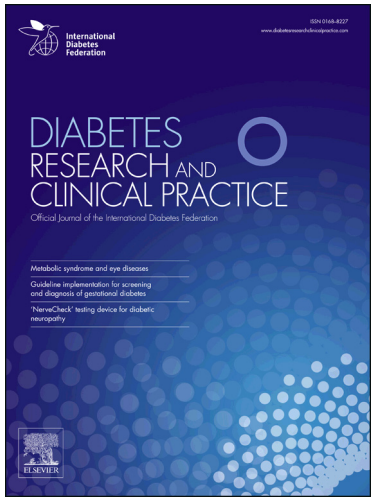
Ikäheimo TM

Elsevier BV

http://doi.org/10.1016/j.diabres.2017.04.022



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PII: S0168-8227(17)30701-5
DOI: http://dx.doi.org/10.1016/j.diabres.2017.04.022
Reference: DIAB 6947

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 15 September 2015
Revised Date: 7 March 2017
Accepted Date: 21 April 2017

Please cite this article as: T.M. Ikäheimo, J. Jokelainen, J. Hassi, L. Hiltunen, S. Keinänen-Kiukaanniemi, T. Laatikainen, P. Jousilahti, M. Peltonen, L. Moilanen, J. Saltevo, S. Näyhä, Diabetes And Impaired Glucose Metabolism Is Associated With More Cold-Related Cardiorespiratory Symptoms, *Diabetes Research and Clinical Practice* (2017), doi: http://dx.doi.org/10.1016/j.diabres.2017.04.022

DIABETES AND IMPAIRED GLUCOSE METABOLISM IS ASSOCIATED WITH MORE COLD-RELATED CARDIORESPIRATORY SYMPTOMS

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Word count: 4721 words, including narrative text, three tables and figure legends (excluding references, abstract), + 1 figure and 1 supplementary figure

ABSTRACT

Aims: Diabetes and impaired glucose metabolism cause metabolic, neural and circulatory disturbances that may predispose to adverse cooling and related symptoms during the cold season. This study assessed the prevalence of cold-related cardiorespiratory symptoms in the general population according to glycaemic status. Methods: The study population consisted of 2436 men and 2708 women aged 45-74 years who participated in the National FINRISK cold sub-studies in 2002 and 2007. A questionnaire assessed cold-related symptoms (respiratory, cardiac, peripheral circulation). Glycaemic status was determined based on fasting blood glucose, oral glucose tolerance tests or reported diagnosis of diabetes and categorized into normal glucose metabolism, impaired fasting blood glucose, impaired glucose tolerance, screening-detected type 2 diabetes and type 2 diabetes. Results: Type 2 diabetes was associated with increased odds for cold-related dyspnoea [Adjusted OR 1.72 (95% CI, 1.28-2.30)], chest pain [2.10 (1.32-3.34)] and respiratory symptoms [1.85 (1.44-2.38)] compared with normal glucose metabolism. Screened type 2 diabetes showed increased OR for cold-related dyspnoea [1.36 (1.04-1.77)], cough [1.41 (1.06-1.87)] and cardiac symptoms [1.51 (1.04-2.20)]. Worsening of glycaemic status was associated with increased odds for cold-related dyspnoea (from 1.16 in impaired fasting glucose to 1.72 in type 2 diabetes, *P*=0.000), cough (1.02 to1.27, *P*=0.032), chest pain (1.28 to 2.10, *P*=0.006), arrhythmias (0.87 to 1.74, *P*=0.020), cardiac (1.11 to 1.99, *P*=0.000), respiratory (1.14 to 1.84, *P*=0.000) and all symptoms (1.05 to 1.66, *P*=0.003). Conclusions: Subjects with diabetes and pre-diabetes experience more cold-related cardiorespiratory symptoms and need instructions for proper protection from cold weather to reduce adverse health effects.

Keywords: cold temperature, symptoms, diabetes, impaired glucose metabolism

1. INTRODUCTION

People who live in the northern hemisphere are recurrently exposed to environmental cold while commuting, at work and during their leisure time [1]. Various cold-related symptoms are common in the general population [2] and are elicited by physiological reactions due to environmental cold exposure [3]. Our previous reports show that cardiovascular and respiratory symptoms are reported manifold during wintertime in persons with a cardiovascular or respiratory disease [4,5]. Cold-related symptoms may predict the worsening of a chronic condition or be an indicator of an undiagnosed disease. At worst, symptoms may predict an increased risk of adverse health events and explain the globally detected higher wintertime morbidity and mortality [6,7].

In 2014, the global prevalence of diabetes mellitus among adults was estimated at 9% [8]. Furthermore, diabetes alone is estimated to account for 15% of deaths related to cardiovascular diseases [9]. Type 2 diabetes (T2D) accounts for around 90% of all cases of diabetes observed worldwide [10]. It often remains undetected, and screening detected cases may account for 30-60% of all cases of type 2 diabetes [11]. A considerable amount of people have prediabetes with a glycaemic state between normal and diabetic, and it is estimated that up to 70% of these may acquire the disease during their lifetime [12]. In Finland, the prevalence of persons with impaired glucose metabolism, which includes type 2 diabetes and pre-diabetic metabolic disturbances, such as impaired fasting glucose and impaired glucose tolerance, was as high as 42.0% in men and 33.4% in women in the aged group of 45–74 years [11].

One may entertain that cold-related symptoms would be particularly common among people with pre-diabetic metabolic conditions or diabetes because the physiological responses to cold may aggravate the course of the underlying metabolic disturbance. A recent review indicates that diabetes is associated with reduced ability to

maintain body temperature during thermal stress (heat, cold) [13]. Impaired functioning of the autonomic nervous system among those with prediabetes and diabetes [14,15] may lead to increased vasoconstriction and elevated blood pressure and mismatch of myocardial oxygen demand and supply, thus eliciting cardiac symptoms. Decreased arterial compliance [16], altered vasomotor control and blood flow to the extremities could result in either enhanced or blunted peripheral circulatory responses [17-19] and associated symptoms in the cold. In addition, peripheral neuropathy [20] can alter both sensory function and the ability to regulate heat loss in the extremities. Decreased insulin sensitivity associated with prediabetes and diabetes may blunt heat production through brown adipose tissue in the cold [21]. Depending on disease progression, the altered neural, metabolic and circulatory disturbances mentioned above may affect thermal, cardiovascular and respiratory responses in a cold environment and lead to various symptoms.

To our knowledge, no population-based information exists on the prevalence of cold-related cardiovascular or respiratory symptoms among persons having diabetes or impaired glucose metabolism. This information may prove useful for predicting and preventing cold-related health outcomes, but may also provide a tool for detecting individuals with impaired glucose metabolism. Our hypotheses were that (1) pre diabetes and/or diabetes are associated with increased reporting of cold-related symptoms and (2) the prevalence of symptoms increases with worsening of glycaemic status. To test these hypotheses, we compared the prevalence of cold-related symptoms among individuals stratified by glycaemic status in a large population-based representative sample in Finland.

2. METHODS

Finland is a subarctic country locating between 60 and 70° N Lat (Fig. S1) in the coastal zone of the Eurasian continent. The climate is partly maritime, partly continental. Winter (daily temperature less than 0°C) is the longest season in Finland, lasting about approximately 100 days in the southwestern Finland and 200 days in the north (Finnish Meteorological Institute, Climate service).

2.1.Study population

The material for the present research is derived from the National FINRISK Study which is a large Finnish population survey on risk factors on chronic, noncommunicable diseases which has been carried out for 40 years since 1972 every five years using independent, random and representative population samples from different parts of Finland. The data from the present study was collected in 2002 and 2007. The information from the sub-studies related to cold exposure, cold-related symptoms and complaints, health and performance were linked with relevant parameters from the main questionnaire inquiring about the respondent's socioeconomic background factors, health behavior and health, as well as to the clinical measurements and glucose tolerance tests.

Data collection was carried out from January to April in six different areas in Finland using random sampling stratified by sex and 10-year age groups. The study areas were 1) the county of North Karelia, 2) the county of North Savo, 3) the cities of Turku and Loimaa and the 11 surrounding municipalities, 4) the cities of Helsinki and Vantaa, 5) the province of Oulu and 6) Province of Lapland (in 2002) (Fig. S1). The target population in each area consisted of men and women aged 25-64-years. In addition, a total of 1336 65-74-year old participants were included in the county of North Karelia and the cities of Helsinki and Vantaa.

The whole population sampled numbered 13,437 in 2002 and 11,953 in 2007 [22]. In 2002, a random sample of 10,256 (76%) participated in the cold sub-study and 6,671 (67%) in 2007, the rest 24% and 33%, respectively, attending a dietary survey. A self-administered questionnaire on cold-related symptoms was delivered to the participants of the cold sub studies and returned by 64% (n=6591, FINRISK 2002) and 60% (n=4007, FINRISK 2007) persons. In our current analyses, we included 5144 participants aged 45-74-years with complete data (both questionnaire information and assessment of glycaemic status) on all variables used.

Both national FINRISK studies have obtained ethical approvals from the Helsinki Hospital District (number 87/2001 for the 2002 and HUS 229/EO/2006 and HUS 229/EO/2006 for the 2007 Study).

2.2.Data collection

Cold-related symptoms were inquired using the Oulu Cold and Health Questionnaire (OCHQ) assessing perceptions, symptoms, and behavior in the cold [4]. The following questions were utilized in this study: Does cold (temperature less than +10 °C) or cold weather give you any of the following symptoms (yes/no): shortness of breath, prolonged cough or coughing bouts, wheezing or increased excretion of mucus from the lungs (termed here as respiratory symptoms), chest pain or cardiac arrhythmias (cardiac symptoms), or cold-related color changes in fingers in the cold (peripheral vascular symptoms).

Data on socioeconomic background factors, health behavior and health was collected by a questionnaire. Respondents who reported having been diagnosed with or treated by a doctor for elevated blood pressure, hypertension, angina pectoris or heart failure during the past 12 months or had suffered myocardial infarction, cerebral stroke,

cerebral hemorrhage or cerebral vascular thrombosis at some time, or had undergone coronary bypass surgery or angioplasty, were classified as having cardiovascular disease (CVD). Questions and categorization of alcohol consumption and smoking is described in detail in previous studies [22,23].

Clinical measurement included assessment of blood pressure which was measured in a sitting position after five minute rest using a mercury sphygmomanometer. An average of three measurements was used in the analyses. Subjects whose blood pressure was equal or exceeded 140/90 mmHg or who reported having being diagnosed and treated with elevated blood pressure/hypertension, where considered as having arterial hypertension (HTN). Participant's height and weight were measured of which their body mass index (BMI) was calculated as kg/m^2 [22].

2.3.Glycaemic status

Assessments of glycaemic status followed the recommendation of the WHO Expert Group for glucose assessments. After an overnight fast, blood samples were drawn for measurement of fasting plasma glucose concentration. The oral glucose tolerance test was performed according to the WHO recommendations [10] to participants without diagnosed type 1 or type 2 diabetes. Fasting and 2-hour samples for measurement of plasma glucose concentrations were drawn into fluoride citrate tubes and centrifuged within 30 minutes. All assays were performed at the Laboratory of Analytical Biochemistry at the Center for Health and Welfare, Helsinki, using Architect ci8200 analyzer (Abbott Laboratories, Abbott Park, IL). Plasma glucose was determined with a hexokinase method (Abbott Laboratories, Abbott Park, IL).

Those respondents who reported ever been diagnosed by a doctor for having diabetes (FINRISK 2002) or type 2 diabetes (FINRISK 2007) were defined as having

type 2 diabetes. We identified at total of 23 (FINRISK 2002) and 29 (FINRISK 2007) respondents having type I diabetes and those were excluded from our analyses. Glycaemic status was classified according to the WHO 1999 criteria [10]. Thus, individuals without earlier diagnosis of type 2 diabetes but having fasting glucose ≥ 7.0 mmol/L or 2-hour plasma glucose ≥11.1 mmol/L were classified as having screening detected type 2 diabetes. Those with 2-hour plasma glucose ≥7.8 and < 11.1 mmol/L, and fasting plasma glucose < 7.0 mmol/L were classified as having impaired glucose tolerance. Impaired fasting glucose was defined as fasting plasma glucose ≥6.1 mmol/L but < 7.0 mmol/L, and 2 hour plasma glucose < 7.8 mmol/L. The subjects not reporting any of the latter conditions, and with normal test results, were categorized in the normal glucose metabolism group.

2.4.Statistical analyses

The prevalence of cold-related symptoms was first calculated for each glycaemic status group (type 2 diabetes, screening detected type 2 diabetes, impaired glucose tolerance, impaired fasting glucose, normal glucose metabolism), and crude ORs, together with their 95% confidence intervals, were obtained by logistic regression, using the normal glucose metabolism group as reference. The ORs were then adjusted for age, gender, BMI, education, smoking, use of alcohol, as well as having HTN or CVD. Interactions of glycaemic status with HTN and CVD were also tested to assess whether the association of cold-related symptoms with glycaemic status differed in individuals with and without HTN and CVD. Linear trend tests were performed to examine whether the ORs in the fully adjusted model changed consistently depending on glycaemic status. Statistical analyses were performed by SAS version 9.2. for Windows (SAS Institute, Inc.; Cary, NC).

3. RESULTS

The characteristics of the subjects are presented in Table 1. Among participants having abnormal glycaemic status, the most common abnormality was those with impaired glucose tolerance (17.4%), followed by impaired fasting glucose (12.9%), screening detected type 2 diabetes (8.8%) and type 2 diabetes (6.1%). 54% of the participants had normal glycaemic status.

Figures 1 summarize the association of cold-related cardiac and respiratory symptoms with glycaemic status in form of crude prevalences and adjusted ORs and show a consistent association for cardiac symptoms and also some association with respiratory symptoms. The ORs for most individual cold-related symptoms increased with worsening glycaemic status (Table 2 and 3). A consistent increase in the fully adjusted ORs was confirmed for cold-related dyspnoea (from 1.16 in impaired fasting glucose to 1.72 in type 2 diabetes, significant test for trend, P=0.000), cough (1.02 to1.27, P=0.032), chest pain (1.28 to 2.10, P=0.006), arrhythmias (0.87 to 1.74, P=0.020), cardiac (1.11 to 1.99, P=0.000), respiratory (1.14 to 1.84, P=0.000) and all cold-related symptoms (1.05 to 1.66, P=0.003). The associations of cold-related symptoms with glycaemic status were not different for respondents having CVD and HTN, since the tests for interaction were all non-significant at 5% level.

Tables 2 and 3 show the associations of individual cold-related cardiovascular and respiratory symptoms according to glycaemic status in form of prevalences and ORs, with the normal glucose group as reference. Overall 4-5% of the participants reported cold-related cardiac, 20% peripheral vascular (finger color changes) (Table 2) and 9-20% respiratory symptoms (Table 3). The most common individual symptoms were dyspnoea, increased mucus production and color changes in fingers which were all reported by one fifth of the respondents.

The crude OR for having cardiac symptoms in the cold was over 2-3-fold in the type 2 diabetes group compared with that in the normal glucose metabolism group, and it was approximately 2-fold in the screening detected type 2 diabetes group (Table 2). For cold-related respiratory symptoms, the crude OR was approximately 1-3-fold in the type 2 diabetes compared with normal glucose metabolism group (Table 3), and it also exceeded unity in the groups of screening detected type 2 diabetes and impaired glucose tolerance. An adjustment for age and sex caused only minor changes in the ORs while some more changes were seen after adjusting for BMI. Further adjustments for education, smoking, alcohol and pre-existing HNT and CVD reduced most ORs to insignificance. However, in those with type 2 diabetes, the fully adjusted ORs remained higher than the reference level for all cold-related [OR: 1.66 (1.29-2.13)], cardiac [(OR: 1.99 (1.34-2.96)] (Fig. 1 a) and respiratory [OR: 1.85 (1.44-2.38)] (Fig. 1 b) symptoms. Out of individual symptoms, dyspnoea showed fully adjusted ORs higher than unity [OR: 1.72 (1.28-2.30)] and so did chest pain [OR: 2.10 (1.32-3.34)] and arrhythmias [OR: 1.74 (1.02-2.97)]. Furthermore, also having screening detected type 2 diabetes increased the odds for dyspnoea [OR: 1.36 (1.04-1.77)], coughing [OR: 1.41(1.06-1.87)] and cardiac symptoms [OR: 1.51 (1.04-2.20)]. Finger color changes in cold were not reported differentially according to glycaemic status.

4. DISCUSSION

Our results show that people having diagnosed diabetes report more cold-related symptoms than those with normal glucose tolerance. Especially cold-related chest pain and dyspnoea were common symptoms among diabetic patients. In addition, already screening detected type II diabetes was associated with increased reporting of cold-related chest pain, dyspnoea and cough. We also showed a consistent increase of many cold-related symptoms with worsening of glycaemic status. Hence, it appears that abnormal metabolic, neural and circulatory functions associated with pre-diabetes and diabetes may predispose to adverse cold-related effects.

The higher occurrence of cold-related cardiorespiratory symptoms is due to the physiological responses related to cold exposure. Cold exposure activates the autonomic nervous system by eliciting vasoconstriction and resulting in increased blood pressure [3]. Cardiac symptoms (chest pain, arrhythmias) may arise from myocardial ischaemia which is due to the increased myocardial oxygen demand with a simultaneous decrease in coronary blood flow which can occur with ageing and some cardiac diseases [24]. Respiratory symptoms, on the other hand, are related to the single and combined effects of airway cooling and drying [25] and the subsequent functional changes in the airways, such as airway narrowing, irritation and increased secretion of mucus. These may manifest themselves as cold-related dyspnoea, coughing, wheezing of breath, as well as increased mucus secretion.

A recent review suggest that those with diabetes have an attenuated capacity to increase metabolic heat production and to decrease skin blood flow during cold stress which complicates the maintenance of stable body temperature [13]. Overall, the physiological responses in cold may be altered in persons with prediabetic metabolic conditions or diabetes due to various reasons. Firstly, the symptoms may arise from

disturbed autonomic function, such as increased sympathetic [14] and reduced parasympathetic activity [15] among those with diabetes, and the consequent effects on cardiac and vascular responses. Sympathetic over-activity elevates blood pressure which is further increased by cold exposure [3] and has been shown to result in myocardial ischemia in the cold among diabetic rats [26]. Cold-related cardiac symptoms among persons with diabetes can also reflect cardiac autonomic dysfunction (reduced heart rate variability) which progress with the duration of the disease and may predispose to cardiac events [27].

Cold-related cardiovascular symptoms among persons with prediabetes or diabetes may also arise from macrovascular complications. Patients with diabetes have decreased arterial compliance and stiffer arteries compared to healthy persons [16] and may therefore be more susceptible to cold. Stiffer arteries combined with ageing [28] can result in aggravated cold-related blood pressure responses and predispose to cardiovascular events.

Diabetic complications in the extremities, such as peripheral vascular disease, as well as peripheral neuropathy alter the ability to regulate heath loss in the extremities [20]. For instance, the vasoconstriction response towards local cooling is impaired in those with diabetes [18,29] which could favor heat loss in a cold environment. On the other hand, tissue perfusion may be decreased in autonomic neuropathy [30] and cooling of the skin may further reduce blood flow to the extremities and their tissues in subjects with diabetes [19], especially in those with cardiovascular autonomic neuropathy [17]. Despite of these suggested pathophysiological changes we did not observe any significant effect of pre-diabetes or diabetes on reporting of cold-related finger color changes. The reasons for the lack of this association remain unknown due to absence of individual clinical information.

The association between prediabetes or diabetes on cold-related respiratory symptoms is less clear. Increased symptom reporting of dyspnoea in the cold among persons with diabetes, and both dyspnoea and cough among persons with screening detected type 2 diabetes could reflect respiratory comorbidity. Also some medication used for respiratory diseases can affect glucose metabolism [31]. On the other hand, reports of dyspnoea may also have a cardiac origin.

In our analyses especially age, gender and BMI weakened the crude association of cold-related symptoms and glycaemic status, indicating confounding by these factors. Our previous population studies have shown that ageing increases reporting of cold-related symptoms [4,5] probably due both to the age-related impairments in thermoregulation [32], and including altered circulatory adjustment capacity [27,33], as well as increased prevalence of chronic diseases which also affect cold-related responses. In addition, women tend to report more symptoms than men, which can be related to increased susceptibility to cooling or reflect gender differences in symptoms reporting [34]. BMI was clearly associated with cold-related symptoms. The association between BMI and CVD probably explains much of the reported symptoms [35]. However, a high BMI alone is related to reduced heat loss [3] but also to a blunted metabolic response in the cold through brown adipose tissue [36] which is considered to have antidiabetic characteristics [37].

4.1.Cold-related symptoms and glycaemic status

We observed that reporting of cold-related dyspnea, chest pain and arrhythmia increased according to worsening of the glycaemic status. It is possible that this reflects the duration and severity of the disease. Prediabetes is associated with normal of slightly elevated blood glucose and gradually developing macrovascular complications,

such as peripheral vascular disease, CVDs and stroke which are more clearly manifested in diabetes [12]. Metabolic defects, such as reduced peripheral glucose disposal, as well as absolute and relative impairment of insulin secretion are observed in impaired fasting glucose and impaired glucose tolerance [12]. Also autonomic neuropathy can occur in the early phases of the metabolic disturbance [15]. Microvascular complications (neuro, retino- and nepfropathies) may develop in prediabetes and occur increasingly with increased glycaemia [12], but they are more common in the diabetic state. The described pathophysiological processes according to glycaemic status are not clear cut and the progression of the disease is related to various individual factors. However, the previously described increased occurrence and severity of the pathophysiological processes from prediabetes to diabetes and onwards could explain the increasing trend of reporting cold-related symptom.

Finally, co-morbid conditions may affect the reporting of cold-related symptoms. Therefore, we examined whether cold-related symptoms were reported differentially according to glycaemic status in persons with HTN and CVD. We did not observe any interaction suggesting that the association between glycaemic status and cold-related symptoms was similar irrespective of having a CVD.

4.2.Validity of the results

The strengths of our study include the representativeness of the sample, good geographical coverage and relatively minor socioeconomic variations throughout the country. Determination of glycaemic status was in most cases based on rigorous measurements and we used questionnaire information only for the assessment of previously diagnosed type 2 diabetes. Self-reported type 2 diabetes may be subject to some information bias. We were also able to take into account a large set of potential

confounders in our analyses. A limitation may arise due to categorization according to different glycaemic groups, which may be subject to some inaccuracies (e.g. the group of subjects with impaired glucose tolerance may include a part of those having impaired fasting glucose) and could have precluded us from detecting some of the differences. In addition, use of medication for chronic conditions can affect symptom reporting, but was not detailed here.

The information produced here is of public health significance for populations residing in the northern hemisphere as it may be an aid in reducing or preventing adverse health effects among persons with disturbed glucose metabolism. Increasing awareness among the public can assist individuals with impaired glucose metabolism or diabetes to protect themselves more carefully from cold weather. Health care personnel in hospitals and community primary care may utilize this information for customized guidance and care of those with prediabetes and diabetes by providing appropriate advice for health risk management in cold conditions. This would include information for proper clothing, level of exercise, nutrition and hydration and any behavioral means to reduce or prevent adverse effects of cold weather.

4.3.Conclusions

In conclusion, diabetes is related to higher occurrence of cardiorespiratory symptoms in the cold. These are reported increasingly with worsening glycaemic status. Overall, the higher occurrence of cold-related symptoms may either predict worsening of a diabetic condition in cold conditions or reveal individuals with impaired glucose metabolism. The importance of the topic is further stressed by the emerging epidemic of diabetes and the ageing of the population.

Role of Funding Sources

This work was supported by The Finnish Work Environment Fund. The funder had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest statement

The authors declare no conflicts of interest.

Acknowledgements

MD, Ph.D. Jouni Lohi is acknowledged for his contribution in processing and interpreting the results of the study.

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FIGURE LEGENDS.

Figure 1 Prevalences (%) and adjusted odds ratios (OR) with their 95% confidence intervals (CI) for cold-related a) cardiac (chest pain, arrhythmias) and b) respiratory (dyspnoea, cough, wheezing, mucus production) symptoms according to glycaemic status. Abbreviations: NG=normal glucose metabolism, IFG=impaired fasting glucose, IGT=impaired glucose tolerance, ST2D=screening detected type 2 diabetes, T2D=type 2 diabetes.

Figure 1S. (supplementary figure to be included to website). Map of the study area.

Table 1. Participant characteristics (FINRISK 2002 and 2007).

	FINRISK 2002		**FINRISK 2007**		**Total**
	Males, n(%)	**Females, n(%)**	**Males, n(%)**	**Females, n(%)**	**n (%)**
Glycaemic status					
NG	642 (47.9)	981 (64.7)	484 (44.1)	714 (59.9)	2821 (54.8)
IFG	225 (16.8)	122 (8.0)	209 (19.1)	107 (9.0)	663 (12.9)

IGT	217 (16.2)	240 (15.8)	197 (18.0)	239 (20.1)	893 (17.4)
ST2D	151 (11.3)	94 (6.2)	120 (10.9)	90 (7.6)	455 (8.8)
T2D	104 (7.8)	80 (5.3)	87 (7.9)	41 (3.4)	312 (6.1)
Age (yrs)					
45-54	393 (29.4)	536 (35.3)	318 (29.0)	365 (30.6)	1612 (31.3)
55-64	561 (41.9)	625 (41.2)	363 (33.1)	423 (35.5)	1972 (38.3)
65-74	385 (28.8)	356 (23.5)	416 (37.9)	403 (33.8)	1560 (30.3)
BMI (k/m2)					
Underweight (<18.5)	1 (0.07)	1 (0.07)	2 (0.2)	5 (0.4)	9 (0.2)
Normal (=18.5-24.9)	313 (23.38)	477 (31.46)	257 (23.4)	401 (33.7)	1448 (28.2)
Overweight (>25-29.9)	657 (49.07)	611 (40.30)	574 (52.3)	446 (37.4)	2288 (44.5)
Obese (>30)	368 (27.48)	427 (28.17)	264 (24.1)	339 (28.5)	1398 (27.2)
Smoking					
No	511 (38.7)	1021 (67.8)	451 (41.4)	809 (68.1)	2792 (54.7)
Stopped over ½ yrs ago	503 (38.0)	255 (16.9)	432 (39.6)	210 (17.7)	1400 (27.4)
Stopped less than ½ yrs ago	22 (1.7)	17 (1.1)	19 (1.7)	9 (0.8)	67 (1.3)
Current smoker	286 (21.6)	213 (14.1)	188 (17.2)	160 (13.5)	847 (16.6)
Use of alcohol					
Light	1209 (91.5)	1445 (96.7)	980 (90.2)	1141 (96.3)	4775 (93.9)
Moderate	73 (5.5)	30 (2.0)	66 (6.1)	23 (1.9)	192 (3.8)
Heavy	39 (3.0)	20 (1.3)	40 (3.7)	21 (1.8)	120 (2.4)
Education					
Low	435 (33.5)	476 (32.4)	286 (26.3)	389 (33.1)	1586 (31.5)
Medium	447 (34.4)	504 (34.3)	403 (37.0)	396 (33.6)	1750 (34.8)
High	418 (32.2)	488 (33.2)	399 (36.7)	392 (33.3)	1697 (33.7)
Past myocardial infarction					
Yes	99 (7.5)	30 (2.0)	51 (4.7)	15 (1.3)	195 (3.8)
Past cerebral stroke					
Yes	58 (4.4)	35 (2.3)	49 (4.5)	33 (2.8)	175 (3.4)
Hypertension					
Yes	425 (32.1)	427 (28.5)	371 (34.4)	384 (32.5)	1607 (31.6)
Cardiac insufficiency					
Yes	79 (6.0)	49 (3.3)	41 (3.8)	33 (2.8)	202 (4.0)
Chest pain in exerction (angina pectoris)					
Yes	123 (9.3)	71 (4.7)	44 (4.1)	42 (3.6)	280 (5.5)
Total	1339 (55.0)	1097 (45.0)	1517 (56.0)	1191 (44.0)	5144

Abbreviations: NG=normal glucose metabolism, IFG=impaired fasting glucose, IGT=impaired glucose tolerance, ST2D=screening detected type 2 diabetes, T2D=type 2 diabetes.

Table 2. Cold-related cardiovascular symptoms according to glycaemic status. Values represent crude and adjusted ORs (95% CI).

Cold-related symptom	**Glycaemic status**			**Model 1**	**Model 2**	**Model 3**	**Model 4**
		n (%)	Crude OR (95% CI)	Adj OR (95% CI)	Adj OR (95% CI)	Adj OR (95% CI)	Adj OR (95% CI)
Chest pain	NG	102 (3.7)	Reference	Reference	Reference	Reference	Reference
	IFG	31 (4.8)	1.30 (0.86 - 1.97)	1.24 (0.82 - 1.89)	1.13 (0.74 - 1.72)	1.25 (0.81 - 1.93)	1.28 (0.82 - 2.01)
	IGT	52 (6.1)	**1.66 (1.18 - 2.34)**	1.31 (0.92 - 1.86)	1.18 (0.83 - 1.68)	1.16 (0.80 - 1.70)	1.20 (0.81 - 1.76)
	ST2D	34 (7.9)	**2.22 (1.48 - 3.31)**	**1.67 (1.11 - 2.53)**	1.37 (0.89 - 2.09)	1.45 (0.93 - 2.27)	1.51 (0.95 - 2.38)
	T2D	34 (11.5)	**3.35 (2.22 - 5.03)**	**2.63 (1.73 - 4.00)**	**2.11 (1.36 - 3.25)**	**2.37 (1.52 - 3.70**)	**2.10 (1.32 - 3.34)**
Total		253 (5.1)					*P=0.006**
Arrhythmias	NG	89 (3.3)	Reference	Reference	Reference	Reference	Reference
	IFG	18 (2.8)	0.86 (0.51 - 1.44)	0.87 (0.52 - 1.47)	0.83 (0.49 - 1.40)	0.91 (0.53 - 1.55)	0.89 (0.51 - 1.53)
	IGT	49 (5.8)	**1.80 (1.26 - 2.57)**	**1.47 (1.02 - 2.12)**	1.39 (0.96 - 2.01)	1.36 (0.92 - 2.01)	1.37 (0.92 - 2.04)
	ST2D	25 (5.9)	**1.84 (1.16 - 2.90)**	1.48 (0.93 - 2.36)	1.32 (0.82 - 2.15)	1.41 (0.86 - 2.31)	1.43 (0.86 - 2.36)
	T2D	22 (7.5)		**2.01 (1.23 - 3.30)**	**1.78 (1.07 - 2.97)**	**1.91 (1.13 - 3.22)**	**1.74 (1.02 - 2.97)**
			2.39 (1.47 - 3.87)				
Total		203 (4.1)					*P=0.020**
Finger color changes	NG	563 (20.6)	Reference	Reference	Reference	Reference	Reference
(peripheral vascular)	IFG	126 (19.5)	0.94 (0.76 - 1.16)	0.92 (0.74 - 1.14)	1.00 (0.80 - 1.25)	0.96 (0.77 - 1.21)	0.98 (0.78 - 1.23)
	IGT	157 (18.1)	0.86 (0.70 - 1.04)	0.79 (0.65 - 0.97)	0.88 (0.72 - 1.08)	0.85 (0.69 - 1.04)	0.86 (0.70 - 1.06)
	ST2D	83 (19.2)	0.92 (0.71 - 1.18)	0.83 (0.64 - 1.08)	1.01 (0.77 - 1.32)	0.96 (0.73 - 1.27)	0.99 (0.75 - 1.31)
	T2D	60 (19.9)	0.96 (0.71 - 1.30)	0.88 (0.65 - 1.19)	1.09 (0.80 - 1.48)	1.12 (0.81 - 1.54)	1.09 (0.79 - 1.51)
Total		989 (19.9)					

Models adjusted for Model 1: age and gender; Model 2: previous and BMI; Model 3: previous and education, smoking, use of alcohol and study area; Model 4; previous and including HTN and CVD. Abbreviations: NG=normal glucose metabolism, IFG=impaired fasting glucose, IGT=impaired glucose tolerance, ST2D=screening detected type 2 diabetes, T2D=type 2 diabetes. * From linear trend test.

Table 3. Cold-related respiratory symptoms according to glycaemic status. Values represent crude and adjusted ORs (95% CI).

Cold-related symptom	Glycaemic status			Model 1	Model 2	Model 3	Model 4
		n (%)	Crude OR (95% CI	Adj OR	Adj OR	Adj OR	Adj OR
Dyspnoea	NG	456 (16.5)	Reference	Reference	Reference	Reference	Reference
	IFG	123 (19)	1.18 (0.95 - 1.48)	1.34 (1.07 - 1.67)	1.16 (0.92 - 1.46)	1.17 (0.93 - 1.48)	1.16 (0.91 - 1.47)
	IGT	192 (22)	**1.42 (1.18 - 1.72)**	**1.33 (1.10 - 1.62)**	1.13 (0.93 - 1.38)	1.15 (0.93 - 1.41)	1.13 (0.92 - 1.39)
	ST2D	122 (27.3)	**1.90 (1.50 - 2.39)**	**1.89 (1.49 - 2.40)**	**1.40 (1.09 - 1.80)**	**1.39 (1.07 - 1.80)**	**1.36 (1.04 - 1.77)**
	T2D	101 (33.2)	**2.51 (1.94 - 3.26)**	**2.56 (1.96 - 3.35)**	**1.88 (1.42 - 2.48)**	**1.88 (1.41 - 2.50)**	**1.72 (1.28 - 2.30)**
Total		994 (19.8)					*P*=0.000*
Prolonged or bouts of coughing	NG	374 (13.6)	Reference	Reference	Reference	Reference	Reference
	IFG	88 (13.8)	1.02 (0.79 - 1.31)	1.09 (0.84 - 1.40)	1.00 (0.78 - 1.30)	1.00 (0.77 - 1.31)	1.02 (0.78 - 1.32)
	IGT	145 (16.9)	**1.29 (1.04 - 1.58)**	**1.24 (1.00 - 1.53)**	1.12 (0.90 - 1.40)	1.11 (0.89 - 1.40)	1.10 (0.88 - 1.38)
	ST2D	93 (21.5)	**1.74 (1.35 - 2.24)**	**1.72 (1.33 - 2.24)**	**1.45 (1.11 - 1.90)**	**1.44 (1.09 - 1.90)**	**1.41 (1.06 - 1.87)**
	T2D	58 (19.7)	**1.56 (1.14 - 2.11)**	**1.56 (1.14 - 2.13)**	**1.29 (0.93 - 1.78)**	1.36 (0.98 - 1.90)	1.27 (0.91 - 1.77)
Total		758 (15.3)					*P*=0.032*
Wheezing of breath	NG	188 (6.9)	Reference	Reference	Reference	Reference	Reference
	IFG	63 (9.9)	1.48 (1.10 - 2.00)	**1.49 (1.10 - 2.02)**	1.23 (0.90 - 1.67)	1.23 (0.90 - 1.69)	1.22 (0.89 - 1.68)
	IGT	99 (11.6)	**1.77 (1.37 - 2.28)**	**1.62 (1.25 - 2.10)**	1.28 (0.98 - 1.68)	1.23 (0.93 - 1.63)	1.24 (0.93 - 1.64)
	ST2D	62 (14.5)	**2.27 (1.67 - 3.09)**	**2.07 (1.51 - 2.84)**	1.36 (0.98 - 1.90)	1.33 (0.94 - 1.87)	1.26 (0.89 - 1.79)
	T2D	46 (15.9)	**2.54 (1.79 - 3.60)**	**2.33 (1.64 - 3.33)**	**1.49 (1.03 - 2.16)**	**1.50 (1.03 - 2.20)**	1.42 (0.96 - 2.09)
Total		458 (9.3)					
Increased mucus production	NG	515 (18.8)	Reference	Reference	Reference	Reference	Reference
	IFG	116 (18.3)	0.97 (0.77 - 1.21)	0.95 (0.76 - 1.19)	0.93 (0.74 - 1.17)	0.89 (0.70 - 1.12)	0.89 (0.70 - 1.12)
	IGT	179 (20.9)	1.14 (0.94 - 1.38)	1.05 (0.86 - 1.27)	1.02 (0.84 - 1.24)	1.02 (0.83 - 1.25)	1.04 (0.85 - 1.28)
	ST2D	99 (22.8)	**1.28 (1.00 - 1.63)**	1.15 (0.89 - 1.47)	1.10 (0.85 - 1.42)	1.05 (0.81 - 1.38)	1.05 (0.80 - 1.37)

Cold-related symptom	Glycaemic status			Model 1	Model 2	Model 3	Model 4
		n (%)	Crude OR (95% CI	Adj OR	Adj OR	Adj OR	Adj OR
	T2D	75 (25.2)	**1.45 (1.10 - 1.92)**	1.32 (0.99 - 1.75)	1.25 (0.94 - 1.68)	1.30 (0.96 - 1.75)	1.31 (0.97 - 1.77)
Total		984 (19.8)					

Models adjusted for Model 1: age and gender; Model 2: previous and BMI; Model 3: previous and education, smoking, use of alcohol and study area; Model 4; previous and including HTN and CVD. Abbreviations: NG=normal glucose metabolism, IFG=impaired fasting glucose, IGT=impaired glucose tolerance, ST2D=screening detected type 2 diabetes, T2D=type 2 diabetes. *From linear trend test.

Highlights

- Diabetes is a strong determinant for the occurrence of cardiorespiratory symptoms during the cold season.
- People with impaired glucose metabolism report more cold-related cardiorespiratory symptoms.
- Subjects with diabetes and pre-diabetes need instructions for proper protection from cold weather.

Figure

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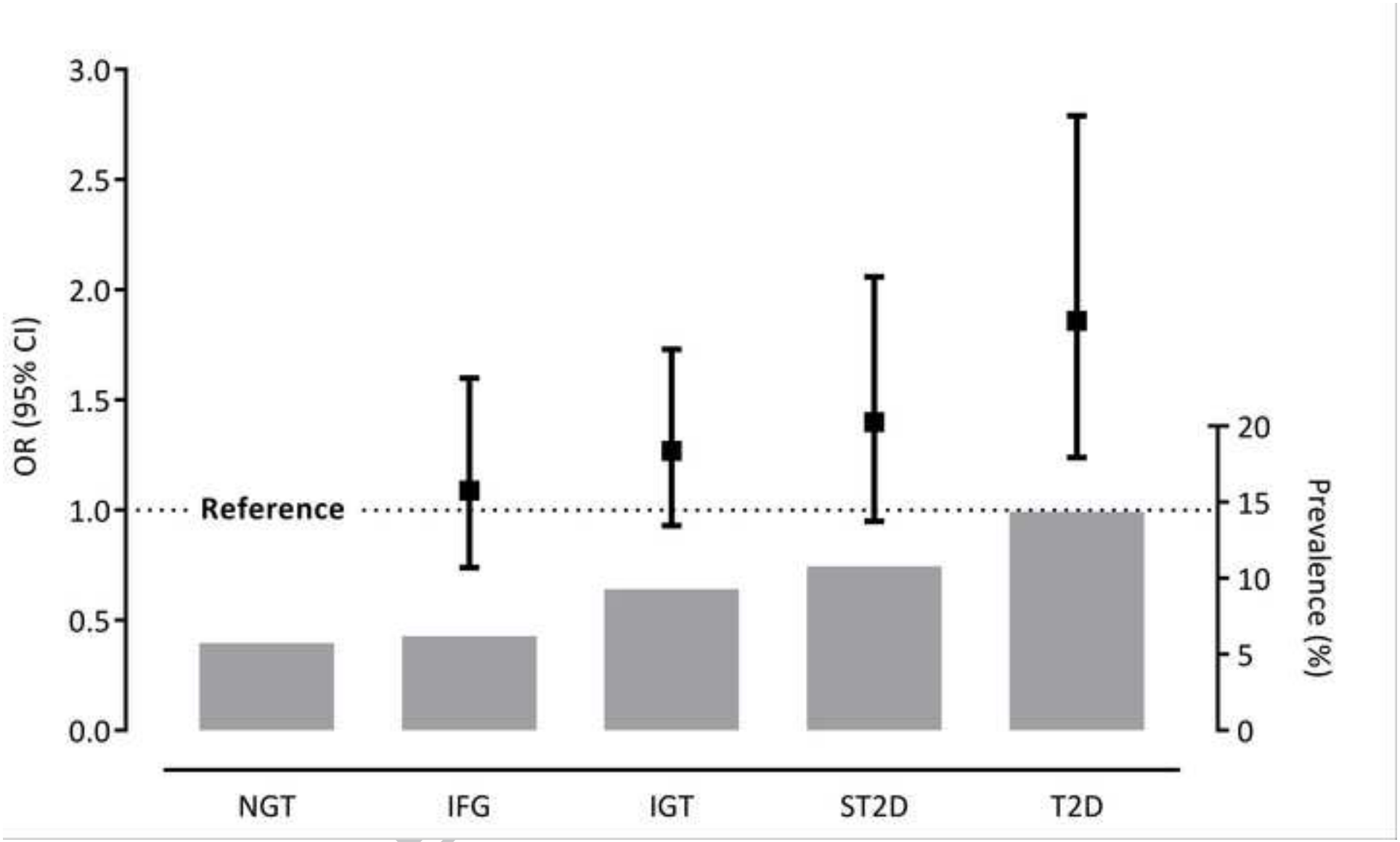

Figure

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