Glycemic status and effect on mortality: multifactorial prevention programme for cardiovascular disease in Finnish primary care

Susanna M. Kuneinen[a,b], Hannu Kautiainen[c,d], Mikael O. Ekblad[a], Päivi E. Korhonen[a]

[a] Department of General Practice, University of Turku and Turku University Hospital, Turku, Finland

[b] Pihlajalinna Plc, Finland

[c] Folkhälsan Research Center, Helsinki, Finland

[d] Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland

Corresponding author:

Susanna Kuneinen, MD

Address: Department of General Practice, 20014 University of Turku, Finland

E-mail address: smkune@utu.fi

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ABSTRACT

Aims

To compare 13-year mortality rates in normoglycemic, prediabetic and diabetic subjects attending a community-based screening and intervention programme.

Methods

Population survey identified 2569 cardiovascular disease (CVD) white risk subjects aged 45-70 years and without manifested CVD or diabetes. Oral glucose tolerance test was performed, and multifactorial intervention was provided. Effect of glycemic status on mortality was estimated in models adjusted for age, gender, education years, smoking, body mass index, mean arterial pressure, total cholesterol, and physical activity.

Results

Of the subjects, 2055 (77%) were normoglycemic, 380 (14%) had prediabetes and 224 (9%) diabetes. Compared to the normoglycemic group, the fully adjusted hazard ratios (HR) for all-cause mortality were 1.34 (95% CI: 0.98 to 1.83) in the prediabetes group and 2.31 (95% CI: 1.62 to 3.31) in the diabetes group. Standardized mortality rates were 0.63 (95% CI: 0.54 to 0.73), 0.91 (95% CI: 0.69 to 1.18), and 1.55 (95% CI: 1.19 to 2.02) in the normoglycemic, prediabetes, and diabetes groups, respectively. The most common cause of death was cancer (42% of all deaths), followed by CVD (28%).

Conclusions/interpretation

Screen-detected diabetes carries a substantial risk of death even after primary care intervention. The pattern of excess mortality has shifted towards cancer deaths.

KEYWORDS

Cardiovascular disease, General Practice, Mortality, Prediabetes, Screening, Type 2 diabetes

1. INTRODUCTION

Over the past 20 years, the global rise in obesogenic lifestyles and ageing population have more than tripled the prevalence of type 2 diabetes [1]. The number of individuals affected by diabetes has been estimated to reach 700 million by 2030 [1]. Type 2 diabetes associates with significant complications, such as kidney failure and cardiovascular disease (CVD), and 1.15 to 1.80 times higher risk of all-cause mortality compared to people without diabetes [2-4]. It is typical that type 2 diabetes has a long subclinical phase and the diagnosis is postponed for several years [5]. Thus, some diabetes associated comorbidities are present already at clinical diagnosis [6]. It has been proposed that early diagnosis and treatment of type 2 diabetes might be beneficial in reducing CVD risk of diabetic individuals [7]. However, it is uncertain if population-based screening for type 2 diabetes has an effect on mortality [8, 9].

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are high-risk precursory conditions for diabetes, also referred as prediabetes. The condition is defined by glycemic levels higher than normal but lower than the diagnostic thresholds for diabetes [10]. Depending on the definition used, up to 70% of prediabetics will develop type 2 diabetes within 10 years [11]. Prediabetes has been associated with increased all-cause mortality and CVD both in the general population and in subjects with atherosclerotic CVD [6].

In this longitudinal cohort study, we examined the effect of a community-based CVD and type 2 diabetes screening and intervention programme [12] on mortality during the 13-year follow up. Specifically, we compared the risk of all-cause mortality and causes of death between three groups of cardiovascular risk subjects: those with screen-detected diabetes, those with screen-detected prediabetes and those who were normoglycemic according to the oral glucose tolerance test (OGTT) at baseline. Mortality rates in these study groups were also compared to the mortality rate of the general population in Finland.

2. SUBJECTS, MATERIALS AND METHODS

A population survey, the Harmonica Project (Harjavalta Risk Monitoring for Cardiovascular disease), was conducted in the towns of Harjavalta and Kokemäki in Southwest Finland from August 2005 to September 2007. All home-dwelling inhabitants aged 45-70 years (6013 eligible

inhabitants on 31.12.2007) without previously diagnosed diabetes or CVD were invited to participate in the project. An invitation to the project, a cardiovascular risk factor survey, a tape for the measurement of waist circumference (WC), and a type 2 diabetes risk assessment questionnaire (FINDRISC, Finnish Diabetes Risk Score, available from www.diabetes.fi/english) [13] were mailed to every eligible home-dwelling inhabitant. The invited subjects were instructed to fill in the risk factor survey and mail it back to the public health centre if they were willing to participate in the project.

The respondents were eligible if they reported one or more of the following CVD risk factors:

- the latest measured blood pressure (BP) ≥140/90 mmHg
- use of antihypertensive medication
- history of gestational diabetes or hypertension
- first-degree family members' history of coronary heart disease, myocardial infarction or stroke (age ≤55 years if male, ≤65 years if female)
- FINDRISC ≥12 points in Harjavalta (an estimated 1 in 6 will develop diabetes within 10 years) or ≥15 points (1 in 3 will develop diabetes within 10 years) [13] in Kokemäki
- WC ≥ 80cm in women and ≥ 94cm in men in Harjavalta

In Kokemäki, high WC without any other risk factors was not used as an inclusion criteria for logistical reasons due to limited financial resources.

Invitations to participate in the study were scheduled so that the time span from the invitation to the nurse´s appointment was approximately two months. None of the participants died before classification into the study groups. Altogether 4450 (74%) of the invited subjects filled in and returned the risk factor survey. Of them, 2752 met the inclusion criteria and attended the intervention i.e., an appointment with a nurse or both nurse and GP. Only the subjects in whom an OGTT was performed (n = 2659) were included in the analysis described in this study. Respondents with previously diagnosed CVD or diabetes were excluded to create a primary prevention cohort. All participants were white, native Finns. Figure 1 illustrates the study design and the formation of the study population. Participation and all the measurements included were free of charge for the subjects.

2.1. Nurse's appointment for all risk subjects

Prior to the appointment with the study nurse, laboratory tests were collected from all the study participants, and a self-administrated questionnaire including details on education, current smoking status, alcohol consumption (Alcohol Use Disorders Identification Test, AUDIT [14], leisure-time physical activity (LTPA), and depressive symptoms (Beck's depression inventory, BDI) [15] was completed.

At the nurse's appointment a physical examination (including anthropometric measurements and BP) was performed. The nurse explained the laboratory test results and gave lifestyle counselling to all subjects personally. The subjects were advised to reduce intake of saturated fat in the diet and to perform LTPA at least 30 minutes per day or four hours per week. Smokers were encouraged to stop smoking, and overweight and obese persons (BMI ≥25.0 kg/m^2) were encouraged to weight reduction of at least 5% [12]. If the test results revealed high CVD risk defined as newly detected IGT or type 2 diabetes, hypertension, metabolic syndrome (MetS), obesity (BMI ≥30.0 kg/m^2) or the ten-year risk of cardiovascular death was ≥5% based on the SCORE (Systematic Coronary Risk Evaluation) system [16], an appointment with the general practitioner (GP) of the project was scheduled within 2-4 months.

2.1.1. Laboratory tests and measurements

Laboratory tests were performed after at least 12 h of overnight fasting. OGTT was performed by measuring fasting blood glucose (FPG) and 2-hour post-load plasma glucose (2hPG) concentrations after ingestion of a glucose load of 75 g of anhydrous glucose dissolved in water. Glucose concentrations were measured from capillary whole blood samples using the HemoCue Glucose 201+ system (Ängerholm, Sweden). The results were converted from capillary whole blood to capillary plasma glucose values by the analyser. Plasma total cholesterol, triglycerides and HDL cholesterol were measured enzymatically (Olympus AU604, Japan). LDL cholesterol was calculated by Friedewald's formula [17].

BP was measured with a calibrated mercury sphygmomanometer by a trained nurse. The measurements were taken in a sitting posture after at least five minutes rest with a suitable cuff placed on the arm. The mean of two BP readings taken at intervals of at least two minutes was used in the study. Mean arterial pressure (MAP) was calculated as diastolic BP + 1/3 x (systolic BP – diastolic BP). If the mean systolic BP was ≥140 mmHg or the mean diastolic BP ≥90 mmHg,

subjects were instructed to use an automatic BP monitor (Omron M4-1, the Netherlands), which was lent to them to execute a one week of home BP monitoring [18].

Height and weight were measured in a standing position without shoes and outer wear. Height was recorded to the nearest 0.5cm and weight to the nearest 0.1kg. Regularly calibrated digital scales were used. WC was measured at the level midway between the lower rib margin and the iliac crest. The tape was held firmly in a horizontal position and the subjects were asked to breathe out gently during the measurement. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

LTPA level was categorized as low (LTPA for ≥30 minutes at a time for maximum of three times a week), moderate (LTPA for ≥30 minutes at a time for four to five times a week), and high (LTPA ≥30 minutes at a time for six or more times a week).

MetS was defined according to the IDF criteria [19].

2.2. GP´s appointment for high-risk subjects

At the appointment with the study GP for persons with high CVD risk, plasma lipids and fasting plasma glucose were retested, and an ECG and laboratory tests were collected also to exclude secondary causes of hypertension, glucose disorders or dyslipidaemia. The GP examined the patients and repeated lifestyle counselling.

Antihypertensive medication was prescribed if systolic BP was ≥160 mmHg or diastolic ≥100 mmHg. In patients with newly detected diabetes or hypertensive target organ damage (albuminuria, left ventricular hypertrophy on ECG), antihypertensive medication was initiated if systolic BP was ≥140 mmHg or diastolic BP ≥90 mmHg. Ongoing antihypertensive medication was intensified if systolic BP was ≥140 mmHg or diastolic ≥85 mmHg (≥80 mmHg in patients with diabetes. For subjects with SCORE ≥ 5 % [16], preventive medication – an antihypertensive drug, a lipid lowering agent or low dose aspirin – was initiated. A follow-up appointment with the study GP was arranged if type 2 diabetes was diagnosed, if new medications were started, or if previous medication was modified. According to the European guidelines on CVD prevention of that time [20] the first treatment in diabetes was professional dietary advice, reduction of overweight and increased physical activity. Drug therapy was to be added if lifestyle counselling did not lead to a sufficient reduction of hyperglycaemia [20].

2.3. Formation of study groups

Glucose regulation was classified according to the WHO 1999 criteria [21]. The study population was divided into three groups according to their glycemic status:

- Normoglycemic group: FPG <6.1 mmol/l and 2hPG <8.9 mmol/l
- Prediabetes group (including IFG and IGT): FPG 6.1-6.9 mmol/l or 2hPG 8.9-12.2 mmol/l
- Diabetes group: FPG ≥7.0 mmol/l or 2hPG ≥12.2 mmol/mol. The diagnosis of diabetes was confirmed with a control fasting plasma glucose value on another day if the fasting plasma glucose on OGTT was ≥7.0 mmol/l but the 2-hour plasma glucose was <12.2 mmol/l.

2.4. Ethical approval

The study protocol and consent forms were reviewed and approved by the Ethics Committee of Satakunta Hospital District. All participants provided written informed consent for the project and subsequent medical research.

2.5. Mortality

Data on mortality was obtained from Statistics Finland. Causes of death were classified according to the ICD, 10th Revision (ICD-10). We report all-cause mortality and proportion of cancer (ICD codes C00-D48) and CVD (ICD codes I00-I99) mortality in the study groups. For each person, the date of the invitation to the Harmonica project was the start date of the observational period. Follow-up time of mortality ended on December 31st, 2018.

2.6. Statistical analysis

Continuous data are presented as mean and standard deviation (SD) or median and interquartile range (IQR) depending on data distribution, while categorical data are presented as rate and proportion. Group differences were investigated through a series of chi-square test and one-way analysis of variances (ANOVA) or logistic models. Sidak multiple comparison procedure was used to correct significance levels for post hoc testing (α 0.05), when appropriate. The bootstrap (10 000 replications) method was used when the theoretical distribution of the test statistics was unknown or in the case of violation of the assumptions (e.g., non-normality). Kaplan-Meier's method was performed to estimate cumulative mortality. Adjusted Kaplan-Meier cumulative mortality rates were estimated using two propensity score-based techniques, stratification and weighting (MMWS, marginal mean weighting through stratification) [22]. MMWS is an extension of propensity score matching (a multiple nominal level treatment) that combines propensity score stratification and

inverse probability of treatment weighting. MMWS is a data pre-processing procedure that reweights a dataset to balance the observed pretreatment characteristics across all treatment groups. Cox proportional hazards regression was used to estimate the crude and adjusted hazard ratios (HR) and their 95% confidence intervals (CIs). We fit three models in these analyses: Model 1 (unadjusted), Model 2 (adjusted for age, gender, education years), and Model 3 (adjusted for age, gender, education years, smoking, body mass index, mean arterial pressure, total cholesterol, leisure-time physical activity, AUDIT score, and cohabiting).

The proportional hazards assumption was tested graphically and by use of a statistical test based on the distribution of Schoenfeld residuals. Relative survival was calculated as the ratio of observed survival to the survival expected from a population matched with regard to age, sex and calendar period using the Ederer II method [23,24]. Relative survival is defined as the observed survival in the patient group divided by the expected survival of a comparable group from the general population. The ratio of observed to expected number of deaths, the standardized mortality ratio (SMR) for all-cause deaths, was calculated using subject-years methods. The expected number was determined by multiplying the person-years of observation by the appropriate mortality rate in the general population according to categories of gender, 1-year age group and calendar (year) period. Statistical comparison between SMRs was made by the Poisson regression models. The Poisson regression models were tested using goodness-of-fit test and the assumptions of overdispersion in models were tested using the Lagrange multiplier test. Probabilities of survival in an age- and gender-matched sample of the general population were calculated from data of the Official Statistics of Finland from Statistics Finland. Normal distributions were evaluated graphically and with the Shapiro–Wilk W test. Stata 17.0 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

3. RESULTS

The study population consisted of 2659 home-dwelling 45-70-year-old subjects (55% females) without previous diagnosis of CVD or diabetes at baseline. Of them, 2055 (77%) subjects were normoglycemic, 380 (14%) had screen-detected prediabetes and 224 (9%) had screen-detected diabetes. Table 1 shows the baseline characteristics of the subjects according to glycemic status.

In the normoglycemic group there were 1395 (68%) subjects regarded as high CVD risk individuals, and 339 (89%) in the prediabetes group. All the subjects in the screen-detected diabetes group were regarded as high-risk.

The normoglycemic subjects were slightly younger and more often females compared to the prediabetes and diabetes group. The normoglycemic subjects had lower levels of metabolic risk factors compared to the other groups, however, the mean total cholesterol level was highest in the normoglycemic group.

The screen-detected diabetics had pronounced metabolic risk factor levels: higher BMI and WC, higher mean systolic BP and MAP, lower mean HDL cholesterol and higher mean triglycerides. They were less educated, and they had higher mean BDI-score than the subjects in the two other groups. When compared to the normoglycemic group, they more often lived alone, were physically less active and used more often antidepressants.

The prediabetic subjects also had higher levels of metabolic risk factors compared to the normoglycemic subjects, but lower levels when compared to the diabetic group. However, smoking was more prevalent, and they had higher mean AUDIT-scores than the normoglycemic subjects.

At baseline, antihypertensive and lipid lowering medication was more often used by subjects with glucose disorders.

3.1. Mortality in the study groups

In the whole cohort, a total of 31,710 person-years were followed up. Median (IQR) follow-up time was 12.3 (11.8 – 12.9) years. There were 289 deaths during the follow-up period: 181 in the normoglycemic group, 54 in the prediabetes group and 54 in the diabetes group. The crude cumulative all-cause mortality over 13 years were as follows: 9.4% (95% CI 8.1 to 10.8) in the

normoglycemic group, 15.0% (95% CI 11.6 to 19.3) in the prediabetes group, and 24.2% (95% CI 19.0 to 30.5) in the diabetes group. The adjusted cumulative all-cause mortality according to glycemic status (p-value for linearity <0.001) is presented in Figure 2.

Table 2 shows the hazard ratios for all-cause mortality in the prediabetes and diabetes groups when the normoglycemic group was set as a reference. Prediabetes was associated with increased mortality risk even when adjusted for sociodemographic factors, but the association was no more significant when further adjustments with major CVD risk factors and lifestyle were made. In the diabetes group, mortality risk was more than two-fold compared to normoglycemic subjects in the fully adjusted model. Hazard ratios for all-cause mortality increased linearly (p <0.001) across the glycemic groups.

3.2. Mortality in relation to standard population

Figure 3 illustrates the relative-survival ratio and standardized mortality ratio (SMR) in the different glycemic groups. In the normoglycemic group the relative survival is higher, in the prediabetes group at the same level and in the diabetes group lower than in the general population. There was a statistically significant difference in the SMR between the study groups (P for linearity <0.001).

Altogether, the most common cause of death was cancer (42% of all deaths), followed by CVD (28%). Table 3 shows the causes of death according to glycemic groups.

DISCUSSION

In this cohort of cardiovascular risk subjects without previously diagnosed CVD or diabetes, all-cause mortality risk during the 13-year follow-up was more than two-fold in the screen-detected diabetics when compared to the normoglycemic subjects. In contrast, prediabetes was not associated with increased mortality risk when sociodemographic factors, lifestyle and major CVD risk factors were taken into account. The most prevalent cause of death was cancer followed by CVD. SMR was lowest in the normoglycemic group, highest in the diabetes group, and at the population level in the prediabetes group. Of note, 60% of the normoglycemic study subjects were high-risk subjects. It seems possible that the used multifactorial intervention managed to lower mortality in the normoglycemic CVD risk persons and stabilize mortality rates in the prediabetes group. However, newly detected diabetes conveys a substantial risk of death even after lifestyle counselling and evidence-based treatments for hypertension and dyslipidaemia.

Our results are in line with previous studies showing that diabetes is associated with nearly twofold higher all-cause mortality risk compared to people without diabetes [2], and screen-detected diabetic subjects have a pronounced CVD risk profile [25, 26]. Type 2 diabetes typically has a long asymptomatic preclinical phase, during which prediabetic glycemic levels are present and the atherosclerotic processes have been proceeding for several years before the clinical diagnosis [27, 28]. Thus, early CVD risk factor modification has been advocated [29]. However, to this date there is still no evidence that early type 2 diabetes diagnosis by screening would reduce population level mortality [8, 9].

The Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION) – Cambridge study [8], the single largest randomized trial to evaluate the outcome of T2D screening in high-risk individuals on population mortality, found no reductions in all-cause or diabetes-related mortality over 10 years. The ADDITION-Europe study found that over a 5-year follow-up, the screen-detected diabetic subjects receiving intensive or routine care had similar mortality rate than the general population of Denmark without diabetes [30]. However, in our study with longer follow-up time, the relative survival of the diabetic subjects was observed to decline sharply 4 years after the screening and intervention. Thus, longer follow-up time might explain the contrary results. To our knowledge, the only population-based study showing significant reduction in all-cause mortality in subjects with screen-detected diabetes compared to subjects with clinically detected diabetes is the ADDITION-Denmark study [7]. The

study showed that a single round of diabetes screening and cardiovascular risk assessment was associated with a 21% reduction in all-cause mortality rate, 20% reduction in cardiovascular mortality and 17% reduction in cancer mortality. The ADDITION-Europe and -Denmark studies both included screening and intervention of other CVD risk factors, such as high cholesterol and hypertension, and included early medical treatment of hyperglycaemia. However, their study populations included also high-risk subjects with history of myocardial infarction and stroke, whereas our study was primary preventive. Also, in our study, antihyperglycaemic medication was not initiated at clinical diagnosis due to the treatment guidelines of that time, which might affect the results. However, as our diabetic subjects were observed to have increased mortality risk, we consider our results to support the current diabetes treatment guidelines that advocate intensive multifactorial CVD risk factor modification for all diabetics [29], including early treatment with prognosis improving antidiabetic medications for diabetic subjects with pronounced cardiorenal risk profile [31].

In the general population, IFG has been associated with a 1.13 increased risk and IGT (defined by the WHO 2006 criteria: 2hPG 7.8. – 11.1 mmol/l) with a 1.25 increased risk of all-cause mortality [6]. In the present study, the subjects with screen-detected prediabetes had higher CVD risk factor levels compared to the normoglycemic group, but with the applied intervention, the mortality rate in the prediabetic group was at the same level as in the normoglycemic group and the general population. Similarly, the Da Qing Diabetes Prevention Outcome Study showed reduced all-cause mortality [HR 0.74 (95%CI: 0.61-0.89)] and fewer CVD deaths with multifactorial lifestyle intervention for subjects with IGT. Our results support the current American and European guidelines that recommend lifestyle changes i.e., weight loss, dietary advice, increased physical activity and stopping smoking, for subjects with prediabetes or increased risk of CVD. Sufficient care for hypertension and dyslipidaemia by evidence-based medication according to individual risk profile is also advised [29,32]. These approaches ultimately aim at reducing the risk of CVD or other vascular complications. The diagnosis of prediabetes is not necessarily essential for efficient risk factor modification, but for some individuals it might serve as a motivational factor [33].

In the present study, the most common cause of death was cancer in all study groups, followed by CVD. The subjects with glucose disorders had 10% higher cancer mortality compared to normoglycemic subjects and the subjects with screen-detected diabetes had over 10% higher CVD mortality compared to the two other groups. In the recent studies from England [34] and Scotland [35] a transition towards cancer as the leading contributor of death in diabetic population has been

found. In the Finnish diabetic population CVD mortality is still the most common cause of death, however, cancer mortality is about 50% higher in subjects with diabetes than in non-diabetic subjects, accounting for 25% of the total mortality [36]. The decreasing CVD mortality in individuals with diagnosed diabetes might be associated with shortening of the time between diabetes onset and clinical diagnosis [5], improved diabetes treatment and intensified simultaneous treatment of other CVD risk factors. Moreover, premature coronary artery disease mortality has declined markedly in Finland and in other Western industrialized countries in the last decades [37]. The prevalence of undiagnosed diabetes has declined in Finland after the national diabetes prevention programme (The Development Programme for the Prevention and Care of Diabetes, DEHKO) was successfully carried out during 2000-2010 with the intention to raise awareness of diabetes and its risk factors [38]. At present, the proportion of unidentified diabetes in the population is 3.1% in men and 1.4% in women [39].

4.1. Strengths and limitations

Our study has some limitations. First, the lack of randomization, thus we could not compare the benefits of screening and intervention in comparison to standard care. Moreover, there may be additional, non-measured factors associated with increased risk of mortality which we could not take into account. Second, the eligibility criterion regarding the home-measured WC was not used in Kokemäki due to financial reasons. Thus, some subjects with prediabetes might have remained unidentified. In Harjavalta, we performed an OGTT to all women with WC ≥80 cm and men with WC ≥90 cm. Although this definition of central obesity was a highly sensitive (sensitivity 91% in women, 81% in men) screening method for glucose disorders, it lacked specificity (specificity 20% in women, 28% in men) [40]. Given the high prevalence of central obesity in general population, screening all these individuals with an OGTT would be an unreasonable demand for primary care. Third, the measurements, including glucose parameters, and CVD risk factor evaluations were only made at baseline. We have no information about the shifts in CVD risk factors and development or resolvement of glucose disorders during the follow-up. Fourth, the newly diagnosed diabetics were not treated with glucose lowering medication at the time of diagnosis, which might reflect to the results and complicates the comparison to other studies. Finally, the primary preventive focus in the selection of the study population disables us from comparing the mortality rate of screen-detected diabetics to subjects with previously diagnosed diabetics.

One of the strengths of the present study is the study population. The study participants comprise a representative sample of the community's apparently healthy subjects at risk for CVD and diabetes.

However, although response rate to the Harmonica Project was quite good, there might have been non-response bias since non-respondents in preventive programmes often have a less healthy lifestyle and may have lower socioeconomic position than respondents [41]. Also, the used intervention was typical for general practice where patients at risk of diabetes are usually screened for and where most patients with glucose disorders are treated. The in-office measurements were reliably made by trained medical staff, and the presence of glucose disorders was verified by retesting prior to the visit with the study GP. The 13-year follow-up time was adequate enough to accumulate a sufficient number of outcome events. Furthermore, the used Finnish registers to obtain the underlying causes of death have high validity [42].

In conclusion, our study shows a difference in mortality risk between white subjects with screen-verified normoglycemia, prediabetes and diabetes. Type 2 diabetes, even when detected early by screening, proposes still a significant risk factor for mortality. However, early detection and enhanced treatment of simultaneous CVD risk factors is shifting the pattern of excess mortality towards cancer in the whole spectrum of glucose disorders. Further studies are needed to clarify the possible preventive and clinical implications.

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5.2. Conflicts of interest

There are no conflicts of interest.

5.3. Contribution statement

PEK and HK had full access to all of the data in the study and take responsibility for the integrity of the data. PEK designed the HARMONICA-study and is the principal investigator. SMK, PEK and HK conceived the study question for this paper. HK was responsible for the statistical methods and analysed the data. SMK and PEK participated in the analysis of the data and SMK drafted the

report. SMK, PEK, HK and MOE participated in the interpretation of the data, the critical revision of the report for important intellectual content and gave final approval for this version to be published.

5. REFERENCES

[1] Saeedi P, Petersohn I, Salpea P et al (2019) Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract 157:107843.

[2] Rao Kondapally Seshasai S, Kaptoge S, Thompson A et al (2011) Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 364(9):829-841.

[3] Barnett KN, Ogston SA, McMurdo MET et al. (2010). A 12-year follow-up study of all-cause and cardiovascularmortality among 10 532 people newly diagnosed with Type 2 diabetes in Tayside, Scotland. Diabetic Medicine 27:1097-1215.

[4] Tancredi M, Rosengren A, Svensson A-M et al (2015) Excess mortality among persons with type 2 diabetes. N Engl J Med 373:1720-32.

[5] Rahman M, Simmons RK, Hennings SH et al (2012) How much does screening bring forward the diagnosis of type 2 diabetes and reduce complications? Twelve year follow-up of the Ely cohort. Diabetologia 55(6):1651-1659.

[6] Cai X, Zhang Y, Li M et al (2020) Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. BMJ 370:m2297.

[7] Simmons RK, Griffin SJ, Lauritzen T, Sandbæk A (2017) Effect of screening for type 2 diabetes on risk of cardiovascular disease and mortality: a controlled trial among 139,075 individuals diagnosed with diabetes in Denmark between 2001 and 2009. Diabetologia 60(11):2192-2199.

[8] Simmons RK, Echouffo-Tcheugui JB, Sharp SJ et al (2012) Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial. Lancet 380(9855):1741-1748.

[9] Peer N, Balakrishna Y, Durao S (2020) Screening for type 2 diabetes mellitus. Cochrane Database Syst Rev 5

[10] World Health Organization (2006) Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of a WHO/IDF consultation.

[11] Beulens J, Rutters F, Rydén L et al (2019) Risk and management of pre-diabetes. Eur J Prev Cardiol 26(2_suppl):47-54.

[12] Korhonen PE, Jaatinen PT, Aarnio PT et al (2009) Waist circumference home measurement - A device to find out patients in cardiovascular risk. European Journal of Public Health 19:95-99.

[13] Lindström J, Tuomilehto J (2003) The Diabetes Risk Score. Diabetes Care 26(3):725-731.

[14] Babor TF, de la Fuente JR, Saunders JGM (1989) AUDIT: the alcohol use disorders identification test: guidelines for use in primary healthcare. WHO/MNH/DAT 89.4, Geneva: World Health Organization.

[15] Beck A, Rush A, Shaw B, Emery G (1979) Cognitive therapy of depression. Guilford Press, New York.

[16] Conroy RM, Pyörälä K, Fitzgerald AP et al (2003) Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. European Heart Journal 24:987-1003.

[17] Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge. Clinical Chemistry 18:499-502.

[18] Parati G, Stergiou GS, Asmar R et al (2008) European society of hypertension guidelines for blood pressure monitoring at home: A summary report of the second international consensus conference on home blood pressure monitoring. Journal of Hypertension 26:1505-1526.

[19] Alberti KG, Zimmet P, Shaw J (2005) The metabolic syndrome - a new worldwide definition. Lancet 366(9491):1059-1062.

[20] De Backer G, Ambrosioni E, Borch-Johnsen K et al (2003) European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). Eur J Cardiovasc Prev Rehabil 10(4):S1-S10.

[21] WHO (1999) Definition, Diagnosis and Classication of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1: Diagnosis and Classication of Diabetes Mellitus. Geneva.

[22] Linden A (2014) Combining propensity score-based stratification and weighting to improve causal inference in the evaluation of health care intervention. J Eval Clin Pract 20:1065-1071.

[23] Dickman P, Adami H (2006) Interpreting trends in cancer patient survival. J Intern Med 260:103-117.

[24] Ederer F, Heise H (1959) Instructions to IBM 650 Programmers in Processing Survival Computations. Methodological note No. 10, End Results Evaluation Section, National Cancer Institute: Bethesda, MD, USA.

[25] Sandbaek A, Griffin SJ, Rutten G et al (2008) Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk. The ADDITION study. Diabetologia 51(7):1127-1134.

[26] Spijkerman AM, Adriaanse MC, Dekker JM et al (2002) Diabetic patients detected by population-based stepwise screening already have a diabetic cardiovascular risk profile. Diabetes Care 25(10):1784-1789.

[27] Harris MI, Klein R, Welborn TA, Knuiman MW (1992) Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care 15(7):815-819.

[28] Glümer C, Jørgensen T, Borch-Johnsen K (2003) Prevalences of diabetes and impaired glucose regulation in a Danish population: the Inter99 study. Diabetes Care 26(8):2335-2340.

[29] Cosentino F, Grant PJ, Aboyans V et al (2020) 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 41(2):255-323.

[30] Griffin SJ, Borch-Johnsen K, Davies MJ et al (2011) Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet 378(9786):156-167.

[31] Buse JB, Wexler DJ, Tsapas A et al (2020) 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 63(2):221-8.

[32] Authors/Task Force Members, Piepoli MF, Hoes AW, Agewall S et al (2016) 2016 European Guidelines on cardiovascular disease prevention in clinical practice. European Heart Journal 37(29):2315-2381.

[33] Korhonen PE, Järvenpää S, Kautiainen H (2014) Primary care-based, targeted screening programme to promote sustained weight management. Scand J Prim Health Care 32(1):30-36.

[34] Pearson-Stuttard J, Bennett J, Cheng YJ et al (2021) Trends in predominant causes of death in individuals with and without diabetes in England from 2001 to 2018: an epidemiological analysis of linked primary care records. Lancet Diabetes Endocrinol 9(3):165-173.

[35] Collier A, Meney C, Hair M et al (2020) Cancer has overtaken cardiovascular disease as the commonest cause of death in Scottish type 2 diabetes patients: A population-based study (The Ayrshire Diabetes Follow-up Cohort study). J Diabetes Investig 11(1):55-61.

[36] Niskanen L, Partonen T, Auvinen A, Haukka J (2020) Trends and predictors in all-cause and cause-specific mortality in diabetic and reference populations during 21 years of follow-up. J Epidemiol Community Health 74(11):950-956.

[37] Jousilahti P, Laatikainen T, Salomaa et al (2016). 40-Year CHD mortality trends and the role of risk factors in mortality decline the North Karelia Project experience. Global Heart 11:207-212.

[38] Finnish Diabetes Association (2003) DEHKO – Development Programme for the Prevention and Care of Diabetes in Finland 2000–2010. Available from https://www.diabetes.fi/files/1108/Programme_for_the_Prevention_of_Type_2_Diabetes_in_Finland_2003-2010.pdf Accessed 5 May 2021.

[39] Koponen P, Borodulin K, Lundqvist A et al (2018) Health, functional capacity and welfare in Finland – FinHealth 2017 study. National Institute for Health and Welfare (THL). Available from http://urn.fi/URN:ISBN:978-952-343-105-8 (abstract in English). Accessed 1 March 2021.

[40] Korhonen PE, Jaatinen PT, Aarnio PT, et al (2009) Waist circumference home measurement – a device to find out patients in cardiovascular risk. Eur J Public Health Jan;19(1):95-9.

[41] Bender AM, Jørgensen T, Helbech B, et al (2014). Socioeconomic position and participation in baseline and follow-up visits: the Inter99 study. Eur J Prev Cardiol;21(7):899–905.

[42] Official Statistics of Finland. 2013. Causes of death [e-publication]. Quality Description: Causes of death 2013.
Available from https://www.stat.fi/til/ksyyt/2013/ksyyt_2013_2014-12-30_laa_001_en.html

TABLES AND FIGURES WITH LEGENDS

Table 1. Baseline characteristics of the study participants. P-value denotes to the statistically significant comparisons between the study groups.

	Glycemic status			
	Normoglycemic (N) N=2055	**Prediabetes (P)** N=380	**Diabetes (D)** N=224	P-value [multiple comparison]
Age, mean, years (SD)	58(7)	59(7)	60(6)	<0.001 [N/P, N/D]
Females, n (%)	1187(58)	185(49)	103(46)	<0.001 [N/P, N/D]
Education years, mean (SD)	10.5(2.7)	10.1(2.5)	9.5(2.5)	<0.001 [N/P, N/D, P/D]
Cohabiting, n (%)	1644(80)	291(77)	159(71)	0.004 [N/D]
Body mass index, kg/m^2, mean (SD)	28.3(4.7)	29.6(5.3)	32.0(5.9)	<0.001 [N/P, N/D, P/D]
Waist circumference, cm, mean (SD)				
Women	91(13)	95(14)	102(16)	<0.001 [N/P, N/D, P/D]
Men	100(11)	102(11)	109(13)	<0.001 [N/P, N/D, P/D]
Current smoking, n (%)	326(16)	87(23)	50(22)	<0.001 [N/P]
AUDIT-score, mean (SD)	4.4(4.6)	5.4(5.5)	5.1(6.1)	<0.001 [N/P]
Leisure-time physical activity level, n (%)				0.002 [N/D]
Low	349(17)	75(20)	54(24)	
Moderate	1035(50)	181(48)	118(53)	
High	671(33)	124(33)	52(23)	
Blood pressure, mmHg, mean (SD)				
Systolic	139(18)	143(20)	149(21)	<0.001 [N/P, N/D, P/D]
Diastolic	84(10)	85(10)	86(12)	<0.001 [N/D]
Mean arterial pressure	102 (11)	104 (12)	107 (14)	<0.001 [N/P, N/D, P/D]
Plasma lipids, mmol/l, mean (SD)				
Total cholesterol	5.44(0.96)	5.18(0.99)	5.25(1.08)	<0.001 [N/P, N/D]
HDL cholesterol	1.58(0.45)	1.48(0.41)	1.39(0.45)	<0.001 [N/P, N/D, P/D]
LDL cholesterol	3.28(0.88)	3.09(0.88)	3.15(0.94)	<0.001 [N/P]
Triglycerides	1.35(0.71)	1.40(0.75)	1.71(0.98)	<0.001 [N/D, P/D]
Plasma glucose, mmol/l, mean (SD)				
Fasting	5.23(0.48)	6.33(0.38)	7.95(2.40)	…

2h glucose	6.92(1.60)	7.95(1.91)	12.59(3.30)	…
BDI score, mean (SD)	5.9(5.6)	6.1(5.3)	7.5(6.5)	<0.001 [N/D, P/D]
Medication, n (%)				
Lipid-lowering	217(11)	74(19)	44(20)	<0.001 [N/P, N/D]
Antihypertensive	605(29)	171(45)	127(57)	<0.001 [N/P, N/D, P/D]
Antidepressant	80(4)	17(4)	18(8)	0.015 [N/D]

Sidak's multiple comparison procedure was used to correct significance levels for post hoc testing between the groups ($p<0.05$); multiple comparison test after overall test established significant differences among the groups.

Table 2. Crude and adjusted hazard ratios for all-cause mortality.

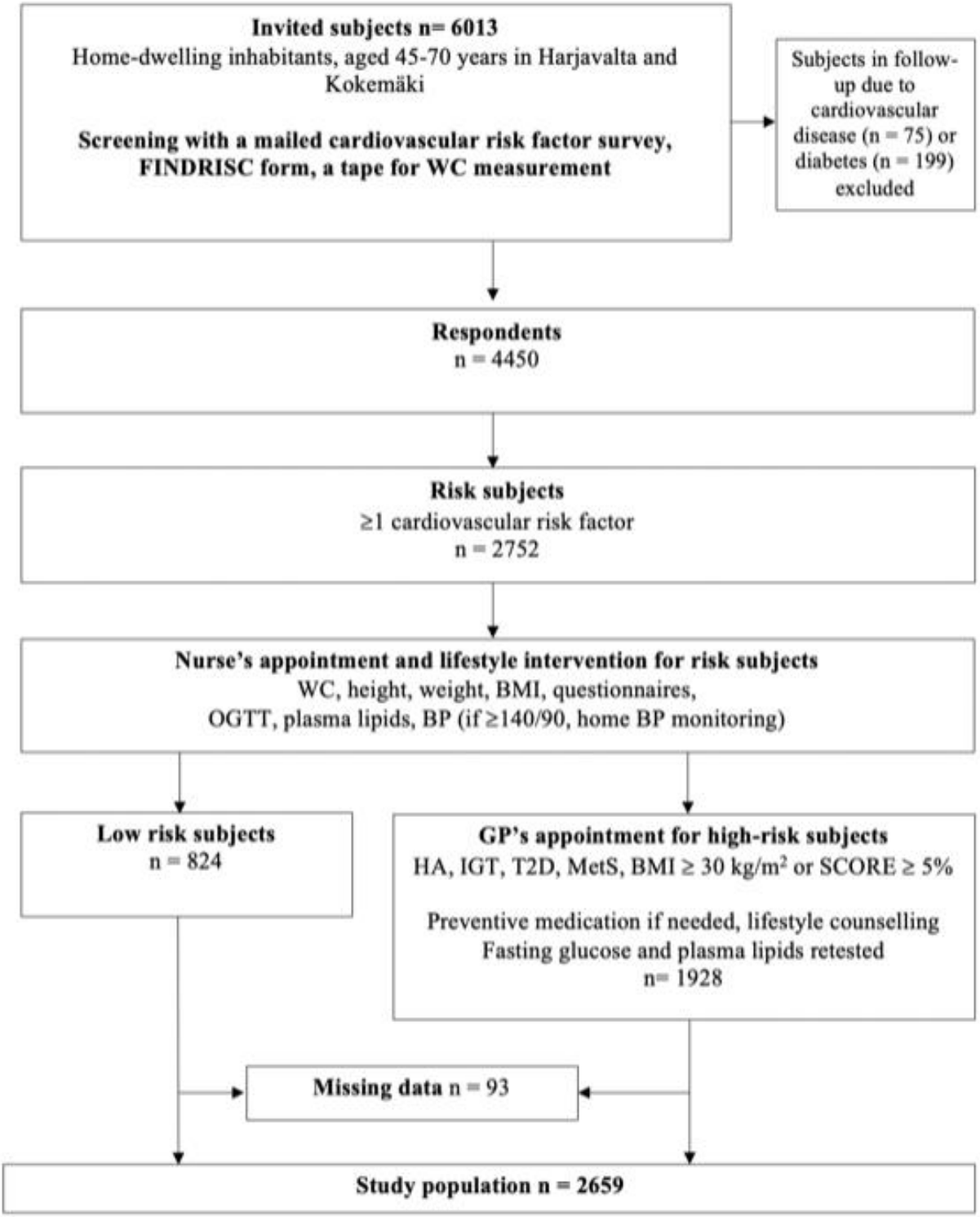
	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Normoglycemic	1.00 (Reference)*	1.00 (Reference)	1.00 (Reference)
Prediabetes	1.67 (1.23 to 2.26)	1.44 (1.06 to 1.95)	1.35 (0.99 to 1.85)
Diabetes	3.09 (2.28 to 4.18)	2.42 (1.78 to 3.29)	2.02 (1.45 to 2.81)
P for linearity	<0.001	<0.001	<0.001

Model 1: crude. Model 2: Adjusted for age, gender, education years. Model 3: Adjusted for age, gender, education years, smoking, body mass index, mean arterial pressure, total cholesterol, leisure-time physical activity, AUDIT score, and cohabiting. *Denominator of Hazard Ratio (HR)

Table 3. Causes of death according to glycemic status.

Cause of death (ICD-10)	**Normoglycemic** n (%) n = 181	**Prediabetes** n (%) n = 54	**Diabetes** n (%) n = 54	**Total** n (%) n = 289
Malignant neoplasms (C00-D48)	70 (38.7)	26 (48.2)	26 (48.2)	122 (42.2)
Diseases of the circulatory system (I00-I99)	48 (26.5)	12 (22.2)	21 (38.9)	81 (28.0)
Other	63 (34.8)	16 (29.6)	7 (13.0)	86 (29.8)

Figure 1. Study design and formation of the study population.



T2D: type 2 diabetes; FINDRISC: Finnish Diabetes Risk Score; WC: waist circumference; BP: blood pressure; BMI: body mass index; OGTT: oral glucose tolerance test; HA: hypertension arterialis; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; MetS: metabolic syndrome; SCORE: Systematic Coronary Risk Evaluation system.

Figure 2. Adjusted cumulative mortality according to glycemic status. Adjustments were made for age, gender, education years, smoking, body mass index, mean arterial pressure, total cholesterol and leisure-time physical activity.

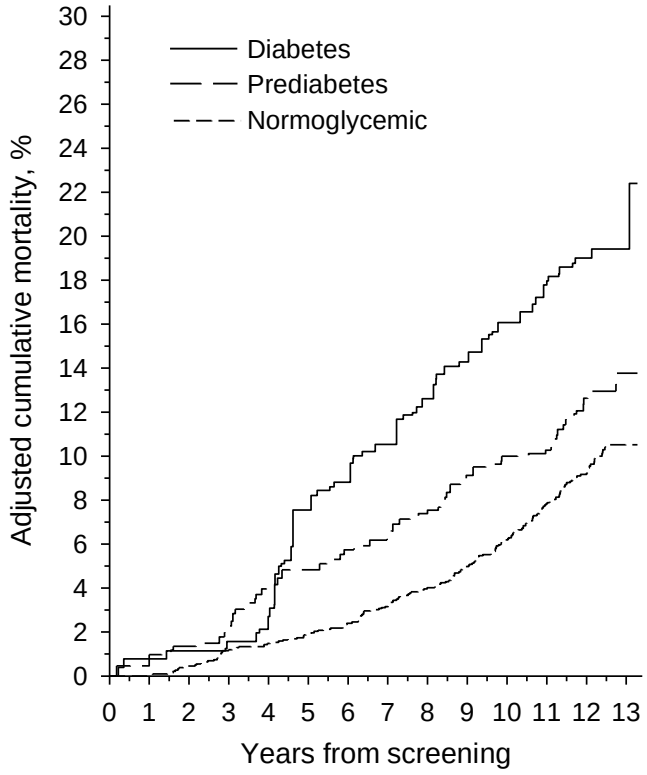


Figure 3. Relative survival over the follow-up period and standardized mortality ratios (SMRs) according to glycemic status during the 13-year follow-up. The dashed line represents the even ratio of observed survival to the survival expected from a population matched with regard to age, sex and calendar period.