Primary Care Diabetes

22-year trends in dysglycemia and body mass index: a population- based cohort study in Savitaipale, Finland

--Manuscript Draft--

Manuscript Number:	PCD-D-21-00001R2
Article Type:	Original article
Keywords:	Type 2 diabetes, dysglycemia, intermediate hyperglycemia, population-based, prospective, cohort study, obesity, blood pressure, primary health care.
Corresponding Author:	Jouko Lauri Saramies, M.D. South Karelia Social and Health care district FINLAND
First Author:	Jouko Lauri Saramies, M.D.
Order of Authors:	Jouko Lauri Saramies, M.D.
	Markku Koiranen
	Juha Auvinen, Professor
	Hannu Uusitalo, Professor
	Esko Hussi, M.D.
	Henna Cederberg, Title of Docent
	Sirkka Keinänen-Kiukaanniemi, Professor
	Jaakko Tuomilehto, Professor
Abstract:	Aims To describe the 22-year observational population-based prospective survey that determined the prevalence and incidence of dysglycaemia, including type 2 diabetes (T2D) and intermediate hyperglycaemia (IH), obesity, hypertension, and disorders of lipid metabolism in the middle-age population in a Finnish municipality. Methods The baseline survey was performed in 1996-1999, and the follow-ups in 2007-2008 and 2018-2019, respectively. The surveys comprised questionnaires, clinical measurements, 2-hour oral glucose tolerance test and other biochemistry analyses, and registry data. Results During 22 years the prevalence of T2D quadrupled to 27% and the proportion of normoglycemic people decreased from 73% to 44% while IH increased only slightly. A large proportion of people who died between the surveys were classified as diabetic. There was no change in body mass index but waist circumference increased significantly. Systolic blood pressure increased during follow-up but diastolic blood pressure did not. The mean serum total and LDL-cholesterol decreased in both sexes while HDL-cholesterol and triglycerides remained stable. The proportion of those who had achieved targets in the treatment of dyslipidaemia increased. Conclusions The prospective survey was successful with high participation rates. The progression of dysglycaemia to diabetes with aging was rapid in middle-aged people although BMI did not change.
Suggested Reviewers:	Maria Ines Schmidt maria.schmidt@urfgs.br

	Edith Feskens edith.feskens@wur.nl
	Stefan Söderberg stefan.soderberg@umu.se
	Rafael Gabriel rgabriel@ceiis.org
Response to Reviewers:	

Highlight

A description of the study design and population of the Savitaipale Study in Finland.

A 22-year prospective population-based and cohort study.

The main aim was to assess changes in cardiometabolic factors in middle-aged people

People with normal glucose metabolism rapidly converted to dysglycaemia and diabetes.

BMI remained unchanged, systolic blood pressure increased and lipid values improved.

Conflicts of interest: None declared

22-year trends in dysglycemia and body mass index: a population- based cohort study in Savitaipale, Finland

Jouko Saramies[a,b], Markku Koiranen[b], Juha Auvinen[b,c], Hannu Uusitalo[d,e], Esko Hussi[a], Henna Cederberg[b,f], Sirkka Keinänen-Kiukaanniemi[b,c,g], Jaakko Tuomilehto[h,i]

[a]South Karelia Social and Health Care District, Finland,

[b]Center for Life Course Health Research, University of Oulu, Oulu, Finland

[c]Medical Research Center, Oulu University Hospital, Oulu, Finland

[d] SILK, Department of Ophthalmology, Faculty of Medicine and Health Technology, Tampere University, PL 100, 33014 Tampere, Finland

[e]Tays Eye Centre, Tampere University Hospital, Tampere, Finland

[f]Department of Endocrinology, Abdominal Center, Helsinki University Hospital, Helsinki Finland

[g]Healthcare and Social Services of Selänne, Pyhäjärvi, Finland

[h]Public Health Promotion Unit, Finnish Institute for Health and Welfare, Helsinki, Finland

[i]Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia

22-year trends in dysglycemia and body mass index: a population- based cohort study in Savitaipale, Finland

Jouko Saramies[a,b], Markku Koiranen[b], Juha Auvinen[b,c], Hannu Uusitalo[d,e], Esko Hussi[a], Henna Cederberg[b,f], Sirkka Keinänen-Kiukaanniemi[b,c,g], Jaakko Tuomilehto[h,i]

Affiliations:

[a]South Karelia Social and Health Care District, Finland,

[b]Center for Life Course Health Research, University of Oulu, Oulu, Finland

[c]Medical Research Center, Oulu University Hospital, Oulu, Finland

[d] SILK, Department of Ophthalmology, Faculty of Medicine and Health Technology, Tampere University, PL 100, 33014 Tampere, Finland

[e]Tays Eye Centre, Tampere University Hospital, Tampere, Finland

[f]Department of Endocrinology, Abdominal Center, Helsinki University Hospital, Helsinki Finland

[g]Healthcare and Social Services of Selänne, Pyhäjärvi, Finland

[h]Public Health Promotion Unit, Finnish Institute for Health and Welfare, Helsinki, Finland

[i]Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia

Contact details:

Postal address: Jouko Saramies

Torikatu 34

54800 Savitaipale

Finland

e-mail address: jouko.saramies@fimnet.fi

Abstract

Aims We describe a 22-year prospective observational population-based study that determined the prevalence and incidence of type 2 diabetes (T2D) and intermediate hyperglycaemia (IH), obesity, hypertension, and disorders of lipid metabolism in a middle-age population in the Finnish municipality of Savitaipale.

Methods 1151 people participated in the baseline survey in 1996-1999, following two follow-up examinations, in 2007-2008 and 2018-2019. Follow-up studies comprised clinical measurements, 2-hour oral glucose tolerance test and other biochemistry, questionnaires, and registry data.

Results The prevalence of T2D quadrupled to 27% and the proportion of normoglycemic people decreased from 73% to 44% while IH increased only slightly during the 22-year follow-up. A large proportion of people who died between the surveys were diabetic.

The mean body mass index (BMI) did not, whereas mean waist circumference increased significantly, by 5-6 cm (P=0.001) during the 22 years. Systolic blood pressure increased by 13-15 mmHg from baseline (P=0.0001) but diastolic blood pressure did not. The mean plasma levels of total and LDL-cholesterol decreased 10.8% and 8.9% in women (P=0.001), 21.5% and 22.2% in men (P=0.001), respectively, while HDL-cholesterol and triglycerides remained stable. The proportion of those achieving targets in the treatment of dyslipidaemia increased significantly (P<0.001).

Conclusions In this 22-year prospective follow-up study of in middle-aged Europeans with high participation rates, the progression of dysglycaemia to overt diabetes with aging was rapid, even without a significant change in BMI.

Introduction

The prevalence of diabetes has markedly increased during the past decades [1-9] and its burden as measured by quality-adjusted life years in adults has increased steepest among all major diseases according to a recent global analysis [8]. Diabetes is also an expensive disease; in Finland the costs due to diabetes has been estimated to account for 9% of the total health care costs [10-12] and in the United States among 155 health conditions, diabetes had the highest health care spending in 2013 [13]. The prevalence and incidence of hyperglycaemia increased mainly due to altered lifestyle and aging of populations [14-16]. The consequences of high blood

glucose are significant from a public health point of view as it can cause damage in almost every organ [14,17]. Although genetic factors predispose to the development of type 2 diabetes (T2D), the negative impact of genetic predisposition can be overcome by healthy nutritional habits, normal body weight and physically active lifestyle [18,19].

In the development of T2D, the secretion and effects of insulin on peripheral tissues are decreased resulting in increased fasting blood glucose (impaired fasting glucose, IFG) and postprandial (post-challenge) glucose (impaired glucose tolerance, IGT) and progressively T2D [20]. Dysglycaemia is considered as T2D or intermediate hyperglycaemia (IH), i.e. IFG and IGT. Many studies assessing the prevalence of T2D have been cross-sectional surveys without standard oral glucose tolerance tests (OGTT) and with variable participation rates. Therefore, data from such cross-sectional surveys may be biased without knowledge about the extent that participation bias may affect the results. Cohort studies with repeat examinations and longitudinal data, even on deceased people, will overcome this bias to some extent, since baseline information on non-participants will exist (Supplementary table 3). Obviously, a possibility to some residual unknown bias may remain as always in observational studies.

Many factors associated with an increased risk of T2D are known, but factors associated with the progression from intermediate hyperglycaemia (IH) to overt T2D or reversal to normoglycemia and those associated with persistent normal glucose metabolism throughout the life course are less well understood [21,22]. Obesity is considered the most important risk factor for T2D, due to its direct effects on the risk of T2D via insulin resistance and also since as a composite outcome of unhealthy diet, physical inactivity and sleep disturbances. Obesity is one of the most obvious and easily recognized risk factors for T2D and merits close evaluation when the development of dysglycaemia is studied [22-26]. The prevalence of obesity has also risen markedly in Finland in the past decades with 11% of middle-aged men and 18% of women being obese (body mass index (BMI) ≥30) in 1980 as compared to 21% and 24%, respectively in the 2000s. [27].

However, data from long-term prospective population-based studies evaluating trends in the natural history of glucose metabolism through aging using repeat OGTTs are limited. We carried out a diabetes epidemiology and prevention study in the Savitaipale municipality in Eastern Finland in 1996 -1999 with consecutive OGTTs and a total of 22-year follow-up. Here, we describe the design of the Savitaipale Study, report selected baseline characteristics and present trends in dysglycaemia and its components, blood pressure (BP) and BMI, in the adult population aged 40-

63 years. This 22-year observational population-based study provided an opportunity to examine changes in glucose metabolism and obesity - not only cross-sectionally at different time points – but most importantly also longitudinally. The main purpose of the study was to describe the Savitaipale study design and provide data on changes in glucose metabolism during the 22-year follow-up of the study cohort. In addition, we compared the findings on cardiometabolic factors in the cohort and the entire source population. The results presented in this paper provide data for further hypotheses on temporal trends in changes in glucose metabolism and other outcomes and factors associated with them.

Materials and Methods

Further details are provided in Supplementary information A

We have monitored the levels of non-communicable disease (NCD) risk factors, and the prevalence and incidence of T2D, IFG and IGT and factors associated with them in a rural community of Savitaipale in South-Eastern Finland with 4,200 inhabitants. The baseline survey was carried out in 1996-1999 with 10-year follow-up survey in 2007-2008 and 22-year follow-up in 2018-2019. The baseline and follow-up studies included questionnaires, clinical assessments, blood tests and data from several national health and population registries. In this article the only registers information used were the date of death and use of medication by the time of 10-year follow-up (Figure 1, Supplementary Table 2). Thus, the study comprised two somewhat different data sets: (i) population-based cross-sectional surveys at three time points, and (ii) a cohort of people who participated in the baseline examination and subsequent follow-up examinations.

Baseline survey

The target population comprised 1508 people (708 women, 800 men) born between years 1933 and 1956 and living in Savitaipale on May 27, 1996 (Figure 1). They received invitation letters to the study. 1168 people (77.5%) participated (581, 82.1% women and 587, 73.4% men) (Supplementary Table 4). Glucose status remained unclear in 17 people. The baseline study cohort with full glucose data thus comprised 1,151 persons of whom 249 men and 336 women participated in all three consecutive examinations. The study was carried out with accordance with the Declaration of Helsinki and was approved by the Ethics Review Board of the South Karelia Hospital District.

Questionnaire data. Socio-demographic data, information about health behaviour and lifestyle, history of selected previous diseases, family history of diabetes and

awareness of elevated blood glucose, BP and blood cholesterol was collected by questionnaires.

Clinical measurements. Weight, height, and waist circumference, as well as BP and heart rate were measured. BMI was calculated using the formula: current weight (kg) divided by square of height (m) at baseline.

Laboratory tests. Standardized oral glucose tolerance test was performed. Fasting plasma total cholesterol (TC), high density lipoprotein (HDL-C), triglycerides (TG) and fasting plasma insulin (FPI) were measured. Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula.

National Health Registers such as local health data and national registries such as hospital, drug and pension registers (Figure 1, Supplementary Table 2).

Follow-up surveys

The follow-up surveys used a similar, but not fully identical methodology than the baseline survey with additional assessments.

10-year**.** All 1151 persons who participated at the baseline formed the target population. Of them 75 people (6.5%) had died (21 women and 54 men). Thus, 1076 persons were invited and 919 people participated (85.4%: 486 women [87.6%] and 433 men [83.1%]; mean age 62.8 years; Figure 1)

22-year**.** The target group of the 22-year follow-up survey were all 1,151 persons who participated in the baseline study. Since the baseline survey 245 people (21.3%; 70 women and 175 men) had died, leaving 906 people to be invited to the follow-up survey. Of them, 704 (77.7%; 399 women and 305 men) signed their consent for the participation at least for the register linkage. 637 participated in the actual survey, 627 provided specimens for FPG, blood lipids and glycated haemoglobin (A1C) and 503 people completed an OGTT. 67 people gave a consent for the registry data linkage only due to a poor health general condition or were reluctant to participate.

Statistical methods

The results were analyzed separately in all survey participants and people who participated in all follow-up examinations. At each follow-up visit we recorded frequency (N), mean and t-test p values for differences of means between follow-ups (Table 1). Proportions of recommended optimal cardiovascular factors and chi-square p-value (p) for differences in proportions between baseline and follow-ups

were presented (Table 2). Similarly, at each follow up, glucose tolerance categories according WHO 1999 definition [20] were determined and their frequencies, proportions and their 95% confidence intervals (CIs) tabulated (Table 3). Sankey graphics was used to describe the prevalence of the glucose categories and their changes, and people lost to follow-up from the baseline to the 10-year and 22-year follow-ups (Figure 2). Changes in FPG and two-hour post challenge plasma glucose (2hPG) from baseline to the follow-ups were described with LOESS curves categorized by starting values of fasting glucose (Supplementary Figure 1). Data smoothing for the distributions of FPG and 2hPG at each survey point were described with kernel density function curves. All statistical analyses were performed using SAS 9.4, and OriginPro 2019b.

Results

The demographic results are shown in Table 1. A comparison between participants and non-participants are shown in Supplementary Tables 2 and 3. The mean FPG increased only slightly while the increase in 2hPG was pronounced during the 22-year follow-up (Supplementary Figure 1). The proportion of people with abnormal glucose metabolism and elevated systolic but not diastolic blood pressure increased with age. The proportion of people with normal serum total and LDL cholesterol increased (Table 2). The prevalence of dysglycemia increased over time and the proportion of normoglycaemic people gradually decreased from 72.7% at baseline (95% CI: 70.1-75.3) to 46.5 % (95% CI: 42.6-50.4) at the 22-year follow-up (Table 3). The proportion of people with diabetes doubled from 8% at baseline during the first 10 years and almost doubled to 27% during the second decade. The prevalence of known diabetes increased from 5.1% at baseline to 20.2% at 22 years; the increase was particularly steep during the second decade. The proportion of screen-detected diabetes among all people with diabetes decreased from 63% at baseline to 33% at 22 years. The proportion of IH increased slightly from 18.9% at baseline to 24.0% at 22 years (Table 3, Supplementary Figure 1). The combination of IFG+IGT was relatively uncommon indicating the FPG and 2hPG identified different people with IH.

The Sankey diagram (Figure 2) shows transitions among the glycaemic categories from baseline to the 10-year and further to the 22-year follow-up examinations. Of the non-participants who were alive at the time of the 10-year examination (dropout) or died between baseline and the 10-year examination 19.6% had NGT at

baseline. The corresponding percentage among the non-participants at the 22-year examination who had NGT at the 10-year examination was 28.2%. 29% of the people who did not attend the 22-year examination had not attended the 10-year examination, either. The progression to diabetes was relatively rapid in many people as 59% and 52% of those with new screen-detected diabetes had NGT at the previous examination at the 10-year and 22-year survey, respectively. Of people with isolated IFG, isolated IGT, and combined IGT+IFG at baseline 14%, 25%, and 60%, respectively had diabetes at 10 years and 44%, 67% and 67%, respectively at 22 years (Supplementary Table 1). A large proportion of people who died were classified as having diabetes at the previous survey- 22% and 23% during the first and second period, respectively.

The mean body weight and BMI remained stable during the 10-year follow-up and 22-year follow-up, whereas the mean waist circumference increased in both sexes ($p<0.001$, Table 1). The mean systolic BP (SBP) was stable during the first 10-year period but increased markedly during the second study period while diastolic BP (DBP) virtually did not increase (Table 1). The mean of plasma TC and LDL-C decreased in both sexes while HDL-C and TG remained stable. At the 10-year follow-up 34 % used statins according to the national prescription register. Trends observed in all participants at each survey and in the cohort of people who participated in all follow-up surveys were similar.

Discussion

This 22-year long prospective study differs from many other epidemiological studies as it has combined the repeated cross-sectional surveys in the entire target population and formed a cohort of individuals who participated in all three surveys.

Long intervals between the surveys can be considered both as a strength and weakness. A strength is that long intervals provide an opportunity to observe temporal trends in parameter of interest better than if shorter intervals would have been used. Weaknesses include the limited size of the cohort and selective mortality and non-participation for other reasons such as moving out and poor health especially among the oldest people.

Here, it has been possible to avoid various biases from which many surveys suffer. The surveys included the gold standard 2-hour OGTT in people free of diabetes at each time point in order to investigate the prevalence and incidence of diabetes and dysglycaemia, and the changes in these. The prevalence of diabetes increased

markedly from 8% to 27% over the 22-year period, similarly in men and women. At the same time, the proportion of normoglycaemic people decreased from 73% to 47%. These changes in prevalence were due to the shift of glucose distributions, especially in 2hPG to the right resulting in major changes in the proportion at both ends of the glucose distributions (Supplementary Figure 1). Another Finnish survey in 1985 in men aged 65-84 years found a similar prevalence, approximately 30% [28]. The European collaborative study also based on the OGTT data collected in the 1990s showed a prevalence of diabetes in people aged 50-59, 60-69 and 70-79 years 8%, 18% and 27%, respectively [29], similar to our present results.

It is worth noting that the means of body weight and BMI remained stable during the follow-up in this cohort of relatively old people. In another Finnish population-based studies, mean BMI was 27.2 for women and 27.5 for men aged 55 years and the waist circumference was 86.0 cm and 97.3 cm, respectively [42], comparable to the present study. The prevalence of obesity is increasing globally, but the increase has most markedly taken place in younger generations [23,30]. Nevertheless, the increase in prevalence of diabetes seems largely be due to other factors than obesity *per se*, for instance biological aging, although central obesity, i.e., waist circumference increased. A previous prospective study in elderly Finnish men also showed that obesity did not predict the progression from IGT to T2D [31]. Obviously, our study population aged 22 years during the follow-up period, and to this aim, the impact of aging on the increase in the risk of diabetes to the extent observed will be exploration in the future analyses of our data. Height in both sexes decreased and was approximately 2 cm less at the 22-year follow-up than at baseline, similarly in all participants and cohort attending all three assessments. Height measured in old people may lead to an upward bias when calculating BMI. For instance, using the measured mean values of weight (71kg) and height (160 cm) at 22-year follow-up in women BMI would have been 27.70, while we used height measured at baseline (162 cm) and thus BMI was 27.05, i.e. 2.4% lower. Therefore, we used the baseline height in all calculations.

In the 22-year follow-up examination the mean SBP but not DBP was higher than at baseline and at the 10-year examination. It is known that SBP increases in old age but DBP not [32]. It is also possible that the change in BP measurement device from mercury sphygmomanometer to digital device might have influenced the SBP values; a critique regarding the accuracy of the Omron M4 device has been reported [33].

The fall in plasma total and LDL cholesterol were partly due to the known decrease in older age and partly due to an increased use of statins. For instance, in the 10-year follow-up 34 % used statins according to the national prescription register. Since statins may increase the risk of diabetes slightly [34], it is possible that this may have contributed to the increasing diabetes prevalence. In addition, statin treatment might have reduced mortality among people with diabetes [24,35] which might also lead to increasing prevalence of diabetes over time. These issues will be evaluated in more detail in future analyses of the data.

In a recent analysis of the national sample in the US, the prevalence of diabetes in people aged 45-64 years was 18% and in those aged >65 years 33%, but in the Caucasian population the prevalence estimates were half of those in other ethnicities [7]; it is of note that also A1C was used in diagnosis in addition to FPG and 2hPG. The prevalence based on a cross-sectional assessment is crude and can be a misleading metric of the trajectory of an epidemic, as increasing prevalence of a disease can be either due to the increase in incidence, improved survival, or both. The survival bias will occur because the sickest people die early during the follow-up. In the future we will analyse our data in detail in order to find out the factors contributing to death and causes of death. Diabetes is known to shorten life expectancy [36]. Our present analysis using Sankey diagram showed that a significant proportion of deceased people during both follow-up periods had diabetes. In our study, the lifetime risk of developing diabetes in individuals aged 62–85 years was 27%. Diabetic people who died during the follow-up need to be taken into account, too, when calculating the lifetime risk. In Australia, the lifetime risk of diabetes was higher and estimated to be 30.8% for the people aged 25 years at baseline [36]. In addition, many people who did not participate in the follow-up surveys had severe health issues including diabetes, and we will be able to find out the number of people with diabetes among them once we will receive data from the register linkages. Healthiest people at baseline live longer and are more willing to participate in the study [37,38]. In the future, it will be of interest to evaluate the differences from register data of those who died as compared to those who participated in all three studies. Worldwide, a recent assessment showed that in 2006-2014 increasing trends of diabetes were reported in only 33% of populations, whereas 30% had stable and 36% a declining incidence [39]. Some population-based cohort studies of diabetes and IH applying repeat OGTTs have been previously published elsewhere [44-50] although recent studies and those having such a long, more than 20-years, follow-up are rare. The 10-year incidence of diabetes in people born 1935 in northern Finland was 17.1% as evaluated from 1996 to 2008 [41]. It is also important to determine the duration of diabetes using the medicine purchase register and medical records for further evaluation of mortality and other outcomes.

The proportion of people with known diabetes of all people with diabetes increased over time and the proportion of previously unrecognised, screen-detected diabetes decreased from 63% at baseline to 33% at the 22-year follow-up. This is encouraging and reflects the improvement in diabetes care in this population. The estimate of undiagnosed diabetes for Europe in the 2019 International Diabetes Federation´s Atlas was 41% and elsewhere even higher [16,40]. We will evaluate the quality of care and its trends among people with diabetes in our study population.

In conclusion, the prevalence of T2D quadrupled to 27% and the proportion of normoglycaemic people decreased from 73% to 44% while IH increased only slightly during the 22-year follow-up. A large proportion of people who died between the surveys were classified as diabetic. There was hardly any change in BMI but waist circumference increased significantly. SBP increased, and plasma TC and LDL-C decreased during the 22-year follow-up.

Conflicts of interest None declared

Funding sources
Savitaipale community and health centre,
EVO grants and laboratory support for the South Karelia Central Hospital,
Viipurin tuberkuloosisäätiö, and
Elsemay Björn Fund

Author contributions
JS designed and supervised the Savitaipale Study. MK coordinated the data management and carried out statistical analyses. HU designed and supervised the ophthalmological part of the study. JS and JT drafted the manuscript.
All the authors read, provided comments on and approved the final manuscript.

Appendix A. Supplementary File A and Supplementary Figure 1, Supplementary Tables 1-4.

Keywords Type 2 diabetes, dysglycemia, intermediate hyperglycemia, population-based, prospective, cohort study, obesity, blood pressure, primary health care.

Highlight

This study reports a 22-yearlong prospective population-based cohort-up study that investigated glucose metabolism, obesity, hypertension, and lipid metabolism in middle-aged people at baseline re-examined in two subsequent repeat surveys.

This article will describe the design and study population of the prospective Savitaipale Study in Finland.

People with normal glucose metabolism at baseline were rapidly converted to dysglycemia and diabetes.

Body mass index remained unchanged, systolic blood pressure increased, and plasma lipid values improved.

References

1. Jansson SP, Andersson DK, Svärdsudd K. Prevalence and incidence rate of diabetes mellitus in a Swedish community during 30 years of follow-up. Diabetologia 2007; 50:703-10.
2. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the US population in 1988-1994 and 2005-2006. Diabetes Care. 2009;32(2):287-294.
3. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980. Lancet. 2011;378(9785):31-40.
4. Whiting DR, Guariguata L, Weil C, et al. IDF Diabetes Atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011; 94:311-321.
5. Geiss LS, Wang J, Cheng YJ, et al. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. JAMA 2014; 312:1218-26.
6. Bullard KM, Saydah SH, Imperatore G, et al. Secular changes in US prediabetes prevalence defined by hemoglobin A1c and fasting plasma glucose. Diabetes Care. 2013;36(8):2286-2293.
7. Menke A, Casagrande S, Geiss L, et al. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. JAMA. 2015; 314:1021-9.
8. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. Lancet 2016; 387: 1513–30
9. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396:1204-1222.

10. Kangas T, Aro S, Koivisto VA, et al. Structure and costs of health care of diabetic patients in Finland. Diabetes Care. 1996; 19:494-7.
11. Finnish diabetes association Report (DEHKO). Diabetes costs in Finland 1997-2007. Tampere 2007.
12. Seuring T, Archangelidi O, Suhrcke M, et al. The economic costs of type 2 diabetes: A global systematic review. Pharmacoeconomics. 2015; 33:811-31.
13. Dieleman JL, Baral R, Birger M, et al. US spending on personal health care and public health 1996-2013. JAMA. 2016; 316:2627-2646.
14. Einarson TR, Acs A, Ludwig C, et al. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018; 17:83.
15. Nowakowska M, Zghebi SS, Ashcroft DM, et al. The comorbidity burden of type 2 diabetes mellitus: patterns, clusters and predictions from a large English primary care cohort. BMC Med. 2019; 17:145.
16. Zhang N, Yang X, Zhu X, et al. Type 2 diabetes mellitus unawareness, prevalence, trends and risk factors: National Health and Nutrition Examination Survey (NHANES) 1999-2010. J Int Med Res. 2017; 45:594-609.
17. World Health Organization. Global report on diabetes. World Health Organization, Geneva 2016.
18. Tuomilehto J, Lindstrom J, Eriksson JG, et al: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344:1343–1350
19. Uusitupa MI, Stancáková A, Peltonen M, et al. Impact of positive family history and genetic risk variants on the incidence of diabetes - the Finnish Diabetes Prevention Study. Diabetes Care 2011; 34: 418-23.
20. World Health Organization. 1999. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: Diagnosis and classification of diabetes mellitus. Geneva. WHO Department of noncommunicable disease surveillance. WHO/NCD/NCS/99.2
21. Wu Y, Ding Y, Tanaka Y, et al. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci. 2014;11(11):1185-1200
22. Kolb H, Martin S. Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. BMC Med. 2017; 15:131.
23. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet 2016; 387:1377-96.
24. Jaacks LM, Vandevijvere S, Pan A, et al. The obesity transition: stages of the global epidemic. Lancet Diabetes Endocrinol. 2019;7(3):231-240.

25. Flegal KM, Carroll MD, Kit BK, et al. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA. 2012;307(5):491-497.
26. Hales CM, Fryar CD, Carroll MD, et al. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. JAMA 2018; 319:1723-5.
27. Lahti-Koski M, Seppänen-Nuijten E, Männistö S, et al. Twenty-year changes in the prevalence of obesity among Finnish adults. Obes Rev. 2010;11(3):171-176.
28. Tuomilehto J, Nissinen A, Kivelä S-L, et al. Prevalence of diabetes mellitus in elderly men aged 60 to 84 years in Eastern and Western Finland. Diabetologia 1986; 29: 611-15.
29. DECODE Study Group. Age- and sex-specific prevalence of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care 2003; 26:61-9.
30. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet 2017; 390:2627-2642.
31. Stengård J, Pekkanen J, Tuomilehto J, et al. Changes in glucose tolerance among elderly Finnish men during a five-year follow-up: the Finnish cohorts of The Seven Countries Study. Diabetes Metabolism 1993; 19: 121-9.
32. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet 2017;389:37-55.
33. Naschitz JE, Loewenstein L, R Lewis R, et al. Accuracy of the OMRON M4 automatic blood pressure measuring device. J Human Hypertens 2000:14:423–427.
34. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375:735–742.
35. Mach F, Baigent C, Catapano AL, et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111-188.
36. Magliano DJ, Shaw JE, Shortreed SM, et al. Lifetime risk and projected population prevalence of diabetes. Diabetologia 2008; 51:2179-86.
37. Li Y, Pan A, Wang DD, et al. Impact of healthy lifestyle factors on life expectancies in the US population. Circulation 2018; 138:345-355.

38. Nyberg ST, Singh-Manoux A, et al. Association of healthy lifestyle with years lived without major chronic diseases. JAMA Intern Med. 2020;180:760-768.
39. Magliano DJ, Islam RM, Barr EL, et al. Trends in incidence of total or type 2 diabetes: systematic review. BMJ 2019; 366: l5003.
40. International Diabetes Federation. IDF Diabetes Atlas, 9th Edition 2019, Brussels 2019.
41. Cederberg H, Saukkonen T, Laakso M et al. Postchallenge glucose, A1C, and fasting glucose as predictors of type 2 diabetes and cardiovascular disease: a 10-year prospective cohort study. Diabetes Care 2010; 33:2077-83
42. Mehta N, Stenholm S, Männistö, et al.. Excess body weight, cigarette smoking, and type II diabetes incidence in the national FINRISK studies. Ann Epidemiol. 2020; 42:12-18.
43. Qiao Q, Hu G, Tuomilehto J et al. DECODA Study Group. Age- and sex-specific prevalence of diabetes and impaired glucose regulation in 11 Asian cohorts. Diabetes Care 2003;26:1770-80.
44. de Vegt F, Dekker JM, Jager A, et al. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: The Hoorn Study. JAMA 2001; 25;285(16):2109-13.
45. Söderberg S, Zimmet P, Tuomilehto J, et al. High incidence of type 2 diabetes and increasing conversion rates from impaired fasting glucose and impaired glucose tolerance to diabetes in Mauritius. J Intern Med. 2004;256:37-47.
46. Safari S, Amini M, Aminorroaya A, et al. Patterns of changes in fasting plasma glucose, hemoglobin A1c and the area under the curve during oral glucose tolerance tests in prediabetic subjects: results from a 16-year prospective cohort study among first-degree relatives of type 2 diabetic patients. Acta Diabetol. 2021;58:371-381.
47. Vistisen D, Kivimäki M, Perreault L, et al. Reversion from prediabetes to normoglycaemia and risk of cardiovascular disease and mortality: the Whitehall II cohort study. Diabetologia. 2019;62:1385-1390.
48. Luhar S, Kondal D, Jones R, et al. Lifetime risk of diabetes in metropolitan cities in India. Diabetologia. 2021;64:521-529.
49. Burke JP, Williams K, Haffner SM, et al. Elevated incidence of type 2 diabetes in San Antonio, Texas, compared with that of Mexico City, Mexico. Diabetes Care. 2001;24:1573-8.
50. Pavkov ME, Hanson RL, Knowler WC, et al. Changing patterns of type 2 diabetes incidence among Pima Indians. Diabetes Care. 2007;30:1758-63.
51. 2019 ESC/EAS Guidelines for the management of dyslipida3emias: lipid modification to reduce cardiovascular risk. European Heart Journal 2020;41:111-188.

Table 1. Means and of selected variables. Data are shown for (A) all participants attending in each survey and (B) only people who participated in the baseline and also in both follow-up surveys. N denotes the number of participants for whom data on each variable was available. P_1 is a significance of t-test comparing the mean of 10-year follow-up mean with the baseline mean and p_2 comparing the mean of 22-year follow-up mean with the baseline mean. Glucose and lipids are plasma values.

	A. All participants at each survey								B. Participants who participated in all follow-up surveys					
	Baseline		10-year follow-up			22-year follow-up			Baseline		10-year follow-up		22-year follow-up	
Variable	N	Mean	N	Mean	p_1	N	Mean	p_2	N	Mean	Mean	p_1	Mean	p_2
Age (years), women	576	52.7	486	62.9	.001	389	73.4	.001	340	51.6	62.0	.001	73.2	.001
Age (years), men	575	52.5	433	62.7	.001	298	72.5	.001	250	50.3	60.9	.001	72.1	.001
Weight (kg), women	576	69.8	484	71.2	.093	349	71.3	.086	337	68.7	70.9	.024	71.2	.009
Weight (kg), men	575	81.1	432	82.4	.154	270	81.4	.755	249	80.2	82.5	.056	81.5	.292
Height (cm), women	576	162	484	161	.001	349	160	.001	340	162	161	.001	160	.001
Height (cm), men	575	175	431	174	.006	270	174	.001	250	176	175	.076	174	.001
BMI (kg/m^2), women	576	26.5	484	27.0	.100	349	27.0	.103	337	26.0	26.9	.019	27.0	.007
BMI (kg/m^2), men	575	26.3	432	26.7	.129	270	26.3	.966	249	25.9	26.6	.027	26.3	.215
Waist (cm), women	569	85.6	483	91	.001	349	90.6	.001	335	84.2	90.4	.001	90.5	.001
Waist (cm), men	573	94.6	431	98.4	.001	270	99.0	.001	247	93.1	97.5	.001	98.9	.001
Systolic blood pressure (mmHg), women	571	135	483	133	.080	349	148	.001	335	132	132	.934	147	.001
Systolic blood pressure (mmHg), men	570	135	432	133	.097	270	147	.001	248	131	132	.438	146	.001
Diastolic blood pressure (mmHg), women	571	82	483	80	.005	349	82	.512	335	81	80	.221	82	.172
Diastolic blood pressure (mmHg), men	570	87	432	83	.001	270	84	.001	248	86	83	.001	83	.002
Fasting glucose (mmol/l), women	556	5.4	483	5.6	.001	354	6.0	.001	335	5.3	5.5	.001	5.9	.001
Fasting glucose (mmol/l), men	547	5.4	431	6.0	.001	273	6.1	.001	245	5.3	5.8	.001	6.1	.001
2h glucose (mmol/l), women	553	6.4	436	6.4	.883	290	7.4	.001	276	5.9	5.9	.888	7.3	.001
2h glucose (mmol/l), men	544	6.0	367	6.7	.001	213	7.5	.001	194	5.4	5.9	.001	7.4	.001
Cholesterol (mmol/l), women	574	5.6	479	5.4	.001	354	5.0	.001	336	5.5	5.4	.078	5.0	.001
Cholesterol (mmol/l), men	572	5.6	427	5.1	.001	273	4.4	.001	244	5.6	5.2	.001	4.4	.001
HDL-cholesterol (mmol/l), women	572	1.6	479	1.7	.001	354	1.6	.766	335	1.6	1.7	.001	1.6	.842
HDL-cholesterol (mmol/l), men	569	1.4	427	1.4	.006	273	1.3	.018	244	1.3	1.4	.030	1.3	.192
LDL-cholesterol (mmol/l), women	565	3.5	479	3.2	.001	354	3.1	.001	332	3.4	3.2	.001	3.1	.001
LDL-cholesterol (mmol/l), men	549	3.6	427	3.1	.001	273	2.8	.001	236	3.7	3.2	.001	2.9	.001
Triglycerides (mmol/l), women	573	1.2	479	1.1	.021	354	1.2	.989	335	1.1	1.1	.514	1.2	.089
Triglycerides (mmol/l), men	571	1.5	427	1.3	.003	273	1.2	.001	244	1.5	1.3	.064	1.2	.001

Table 2. Number of people (N) for whom the data on each variable was available and the proportion (%) of participants with the recommended optimal cardiovascular risk factor levels according to the current guidelines [20,51]: Data are shown for (A) all participants attending in each of the three surveys and (B) only people who participated in the baseline and both follow-up surveys.

	A. All participants at each survey								B. Persons who participated in all follow-up surveys							
	Baseline Women 576 Men 575		10-year follow-up Women 486 Men 433			22-year follow-up Women 399 Men 305			Baseline Women 340 Men 250		10-year follow-up Women 340 Men 250			22-year follow-up Women 340 Men 250		
VARIABLE CATEGORY	N	%	N	%	p_1	N	%	p_2	N	%	N	%	p_1	N	%	p_2
Body mass index < 30 kg/m^2, women	576	80.7	484	77.7	0.223	349	79.1	0.543	337	85.8	337	79.5	0.033	337	79.5	0.033
Body mass index < 30 kg/m^2, men	575	83.3	432	82.4	0.708	270	83.3	0.992	249	87.6	249	84.7	0.364	249	83.1	0.163
Systolic blood pressure < 140 mmHg, women	571	63.4	483	72.3	0.002	349	36.7	0.000	335	70.1	335	74.3	0.227	335	37.6	0.000
Systolic blood pressure < 140 mmHg, men	570	63.9	432	72.2	0.005	270	37.8	0.000	248	73.8	248	76.2	0.534	248	39.1	0.000
Diastolic blood pressure < 90 mmHg, women	571	74.8	483	87.8	0.000	349	78.5	0.198	335	78.8	335	87.2	0.004	335	78.8	1.000
Diastolic blood pressure < 90 mmHg, men	570	61.6	432	79.9	0.000	270	72.2	0.003	248	65.7	248	79.8	0.000	248	73.0	0.080
LDL-Cholesterol < 3 mmol/l, women	565	31.2	479	45.3	0.000	354	47.5	0.000	332	32.8	332	42.5	0.010	332	48.2	0.000
LDL-Cholesterol < 3 mmol/l, men	549	25.0	427	43.6	0.000	273	54.9	0.000	236	21.6	236	38.6	0.000	236	53.4	0.000
LDL-Cholesterol < 1.8 mmol/l, women	565	1.6	479	2.1	0.551	354	4.8	0.004	332	2.1	332	1.2	0.362	332	5.1	0.038
LDL-Cholesterol < 1.8 mmol/l, men	549	1.3	427	6.1	0.000	273	15.0	0.000	236	0.8	236	5.5	0.004	236	13.1	0.000
Cholesterol < 5 mmol/l, women	574	26.8	479	33.6	0.017	354	49.4	0.000	336	29.8	336	32.7	0.405	336	49.4	0.000
Cholesterol < 5 mmol/l, men	572	24.7	427	45.7	0.000	273	66.3	0.000	244	23.4	244	41.0	0.000	244	67.2	0.000
Fasting glucose < 5.6/6.1 mmol/l, women*	556	94.2	483	80.7	0.000	354	62.4	0.000	335	95.8	335	84.8	0.000	335	63.6	0.000
Fasting glucose < 5.6/6.1 mmol/l, men*	547	90.5	431	66.6	0.000	273	54.9	0.000	245	92.7	245	74.7	0.000	245	57.6	0.000
Normal glucose regulation, women	576	73.1	470	69.6	0.210	350	50.0	0.000	340	79.1	340	71.8	0.026	340	49.4	0.000
Normal glucose regulation, men	575	72.3	415	54.2	0.000	276	42.0	0.000	250	82.0	250	62.8	0.000	250	44.0	0.000
Nonsmoker, women	561	86.5	444	90.5	0.046	293	94.5	0.000	254	91.7	254	91.3	0.873	254	94.5	0.220
Nonsmoker, men	558	65.2	404	78.0	0.000	233	90.1	0.000	205	79.0	205	83.9	0.204	205	90.7	0.001

*5.6 mmol/l at baseline (whole blood) and 6.1 mmol/l at 10-year and 22-year follow-up (plasma). Glucose and lipids are plasma values

Normal glucose regulation is defined according to the WHO classification [12].

p_1 is a chi-square p-value for testing difference of proportions between baseline and 10-year follow-up and p_2 between baseline and 22-year follow-up respectively.

Table 3. Glucose tolerance categories at baseline and at the follow-up surveys. The number (N) and proportion (%) with 95% confidence interval of normoglycemia (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), both IGT and IFG in the same person (IGT+IFG), previously known diabetes (Known DM) and screen-detected diabetes (New DM) at baseline and the follow-up surveys in (A) all participants and (B) in persons who participated in all follow-up surveys.

	A. All participants at each survey examination						B. Persons who participated in all follow-up examinations			
	Baseline		10-year follow Up		22-year follow Up		Baseline		10-year follow Up	22-year follow Up
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	% (95% CI)	% (95% CI)
NGT	837	72.7 (70.1-75.3)	552	62.4 (59.2-65.6)	291	46.5 (42.6-50.4)	474	80.3 (77.1-83.5)	69.6 (65.9-73.4)	48.3 (44.3-52.4)
IFG	34	3.0 (2.0-3.9)	72	8.1 (6.3-9.9)	25	4.0 (2.5-5.5)	19	3.2 (1.8-4.6)	8.0 (5.8-10.2)	4.3 (2.7-6)
IGT	164	14.2 (12.2-16.3)	79	8.9 (7.0-10.8)	99	15.8 (13-18.7)	70	11.9 (9.3-14.5)	9.0 (6.7-11.4)	16.9 (13.8-19.9)
IGT+IFG	20	1.7 (1.0-2.5)	35	4.0 (2.7-5.2)	26	4.2 (2.6-5.7)	7	1.2 (0.3-2.1)	3.1 (1.7-4.5)	3.8 (2.3-5.4)
Known DM	59	5.1 (3.9-6.4)	93	10.1 (8.2-12.1)	139	20.2 (17.2-23.2)	13	2.2 (1.0-3.4)	6.6 (4.6-8.6)	19.8 (16.6-23.1)
New DM	37	3.2 (2.2-4.2)	54	5.9 (4.4-7.4)	46	6.7 (4.8-8.6)	7	1.2 (0.3-2.1)	3.6 (2.1-5.2)	6.8 (4.7-8.8)

Figure legends

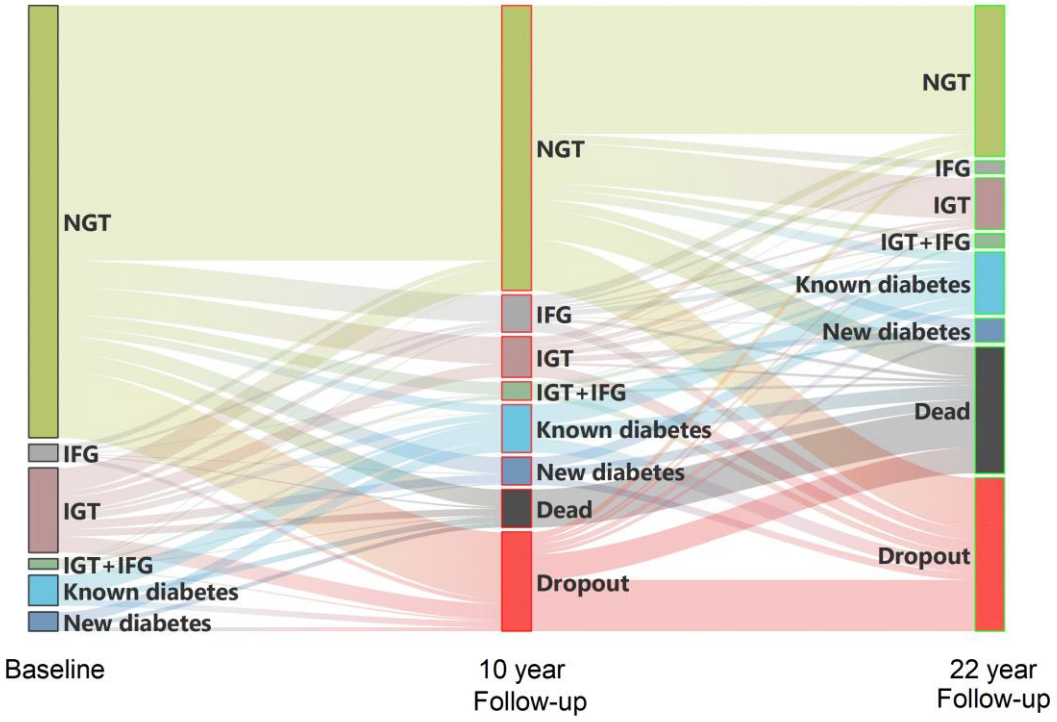
Figure 1. The sources of the registry data and the number of participants in the baseline survey in 1996-1999 and in the follow-up surveys in 2007-2008 and 2018-2019, and the number of people who died during the follow-up and those who did not participate in the survey for other reasons. Participants are individuals who have signed the informed consent for the data collection from different registers.

Color should be used when printing this figure 2!

Figure 2. Changes in glucose metabolic status of all participants during the 22-year follow-up.

The glucose status is divided into groups according WHO 1999 classification [12]: normoglycemia (NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT) and both IFG and IGT in the same person (IGT+IFG). Persons diagnosed with diabetes either in the routine healthcare practice before the survey examination or at the previous survey examination are classified as known diabetes (Known DM) and those diagnosed at the survey examination are classified as new diabetes (New DM). Therefore, people classified New DM or Known DM at baseline are classified as Known DM in the 10-year follow-up. Likewise, people classified New DM or Known DM in the 10-year follow-up are classified Known DM in the 22-year follow-up. Dropout denotes people who did not attend the follow-up examination.

Figure


NGT
IFG
IGT
IGT+IFG
Known diabetes
New diabetes
NGT
IFG
IGT
IGT+IFG
Known diabetes
New diabetes
Dead
Dropout
NGT
IFG
IGT
IGT+IFG
Known diabetes
New diabetes
Dead
Dropout
Baseline
10 year Follow-up
22 year Follow-up

(Supplementary information A)

Materials and Methods

Baseline survey

Questionnaire data. Socio-demographic data, information about health behaviour and lifestyle, history of selected previous diseases and awareness of elevated blood glucose, BP and blood cholesterol. In addition, information about current medication and own birth weight and length and possible problems related to birth. 2.6% and 5.6% of the study population reported using antidiabetic medication and 0.9% and 0.8% diet alone at baseline and 10-year follow-up, respectively. Women were asked about the number of pregnancies and the birth weight of their children, history of diabetes and hypertension during pregnancy and miscarriages.

Clinical measurements. Body weight was measured with a Nordica 6210 floor barometer with an accuracy of 100 g. The height was measured with socks on and without shoes to the nearest half a centimetre with a calibrated ruler attached to the wall. The waist circumference was measured with a flexible tape ruler between the iliac crest and the lowest rib without clothing. The circumference of the hips was measured through a thin underpants clothing with a flexible tape ruler from the plane of the trochanters. BP was measured twice with a Mercurius Stator mercury manometer and a 14x65 cm cuff. SBP and DBP were recorded after the participant was sitting for 15 minutes and the mean of the two measurements was used as SBP and DBP. Heart rate was examined by palpation.

Laboratory tests. Fasting venous blood glucose (FBG) specimen was drawn and analysed with the HemoCue 2010 B-Glucose Analyzer 120710 device. The device was calibrated daily. The FBG result was converted to plasma glucose value using a factor of 1.12 [12]. Serum and plasma samples were collected and centrifuged for further analyses. TC, HDL-C and TG were determined by enzymatic colorimetric method. LDL-C was calculated using the Friedewald formula. FPI was determined by the Microparticle Enzyme Immunoassay method (ABBOTT Laboratories AxSYM® system). An EDTA whole blood sample was collected and stored frozen for DNA extraction. A 2-hour OGTT with 75 g of anhydrous glucose was performed in the persons with no history of diabetes and with FPG <8 mmol/l. We applied WHO 1999 classification for T2D and IH [20]. People who were using glucose lowering drugs were considered as diabetic.

10-year follow-up survey

Questionnaire data. The baseline study questionnaire was repeated. In addition, questionnaires for quality of life with SF-36 and 15D, Beck's depression scale, VF-14 (visual function index), socio-economic status, physical activity habits, sleep, alcohol consumption, and in men International Index of Erectile Function (IIEF-5) were added.

Laboratory tests. Glucose assays were done from venous blood specimen using the HemoCue B-glucose device, which converts and displays the whole blood glucose results automatically to the plasma values. Blood collected at the fasting state was centrifuged and plasma TC, LDL-C and HDL-C were analysed by Colorimetric enzymatic assay (ADVIA 1800®), and plasma TG was analysed by enzymatic colorimetric test. FPI was not determined. All other biochemical tests were performed as at baseline.

Clinical measurements. Weight, height, hip and waist circumference, BP and heart rate measurements were performed as in the baseline survey. BP was measured using mercury sphygmomanometer. For the calculation of BMI in the 10-year follow-up height measured at baseline was used. For ankle-brachial-index (ABI) SBP was measured in the upper limbs and arteria dorsalis pedis and arteria tibialis posterior with a mercury manometer and with a Doppler Atys Microflow S device [31].

Digital color (red, green, and blue light) images from anterior segments of the eyes, red reflexes and retinas were taken by using a retinal camera

Field Code Changed
Field Code Changed
Field Code Changed

22 -year follow-up

Questionnaire data. The same questionnaire as in the 10-year follow-up survey.

Laboratory tests. The same plasma lipid tests as in the 10-year follow-up. FPI and A1C were determined. From the spot urine sample albumin and creatinine were determined and their ratio (ACR) calculated. The 2h-OGTT included plasma glucose measurements at 30 min, 60 min and 120 min.

Clinical measurements. Height, weight, waist and hip circumferences were measured as in the baseline study. For the calculation of BMI in the 22-year follow-up height measured at baseline was used. BP and heart rate were measured twice with the Omron M4-I meter. Body composition was measured with bioimpedance-based Inbody 720 device with participants dressed in light clothes.

The ophthalmologic examination included refraction, best corrected visual acuity, biomicroscopy, tear film stability study (breakup time), ocular fluorescein and

Lissamine Green staining, Schirmer test, measurement of intraocular pressure using applanation and rebound tonometers, assessment of lens opacity by using Lens Opacity Classification System III grading, indirect ophthalmoscopy and imaging the eye by taking anterior segment and retinal photographs and retinal optical coherence tomography.

Regional Health Registers. We are also able to use data from the regional electronic public health register starting in 2010. These data included the number of health care visits, treatment days and other social and health care services and individual costs, and also results of weight and BP measurements at the clinic visits as well as all local laboratory results. In addition, weight and height at birth of 354 participants (145 women and 209 men) were available and for 325 women information regarding pregnancies was available from maternity clinic cards.

Supplementary Table 1. Changes in glucose status in people who had impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or both (IGT+IFG) at baseline. NGT= normal glucose tolerance, DM= diabetes mellitus.

A. Change from the baseline to the 10-year follow-up

Glucose status at baseline	Glucose status at the 10-year follow-up											
	NGT		IFG		IGT		IFG+IGT		DM		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
IFG	11	50.0	6	27.3	-		2	9.1	3	13.6	22	100.0
IGT	45	37.8	11	9.2	26	21.8	7	5.9	30	25.2	119	100.0
IGT+IFG	2	13.3	3	20.0	-		1	6.7	9	60.0	15	100.0
Total	58	37.2	20	12.8	26	16.7	10	6.4	42	26.9	156	100.0

B. Change from the baseline to the 22-year follow-up

Glucose status at baseline	Glucose status at the 22-year follow-up											
	NGT		IFG		IGT		IFG+IGT		DM		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
IFG	8	34.8	1	4.3	2	8.7	2	8.7	10	43.5	23	100.0
IGT	10	12.8	2	2.6	10	12.8	4	5.1	52	66.7	78	100.0
IGT+IFG	1	11.1	-		1	11.1	1	11.1	6	66.7	9	100.0
Total	19	17.3	3	2.7	13	11.8	7	6.4	68	61.8	110	100.0

Supplementary Table 2. Registers in Savitaipale Study

Name of legal register administrator	Used in the present article
Population register center	
Date of death, date of birth, address	Yes
Marital status	No
Finnish Centre for Pensions	
Date of the pension decision, date of the decision on the invalidity pension and the diagnosis leading to the decision.	No
Statistics Finland	
Occupational and socioeconomic status, highest degree of education, causes of death	No
Social Insurance Institution of Finland	
Sickness benefit periods, Visits to a private physician (dates and number of visits), Pensions: type of pension; early retirement period; disabled from (diagnosis of the main disease). Drug treatment reimbursement: Rights for the reimbursement of the specified diseases; date of the right for the reimbursement; diagnosis code. Prescriptions: date of drug purchase; ATC class of the drug; quantity delivered; Costs of drugs and compensation; previous delivery date.	Yes
Finnish Institute for Health and Welfare: Finnish visual disability register, National register of hospital discharges	
Finnish Register of Visual Impairment is recording visual impairment (VI) defined on the basis of WHO criteria information about the onset and degree of visual impairment, the primary and secondary causes of VI, National Register of Hospital Discharges is recording number, duration, and diagnoses of hospital stays. Number, duration, and diagnoses of hospital stays.	No
Local health data	
Numbers of health care treatment cycles and visits, results of all laboratory tests, all diagnoses, results of weighing and blood pressure measurements, prescribed medications. Number of pregnancies of female participants and weight and height of born children. Blood pressure and weight during pregnancies.	No.

Supplementary Table 3. Means of baseline variables of alive people who participated and did not participated in the 10- and 22-year follow-ups

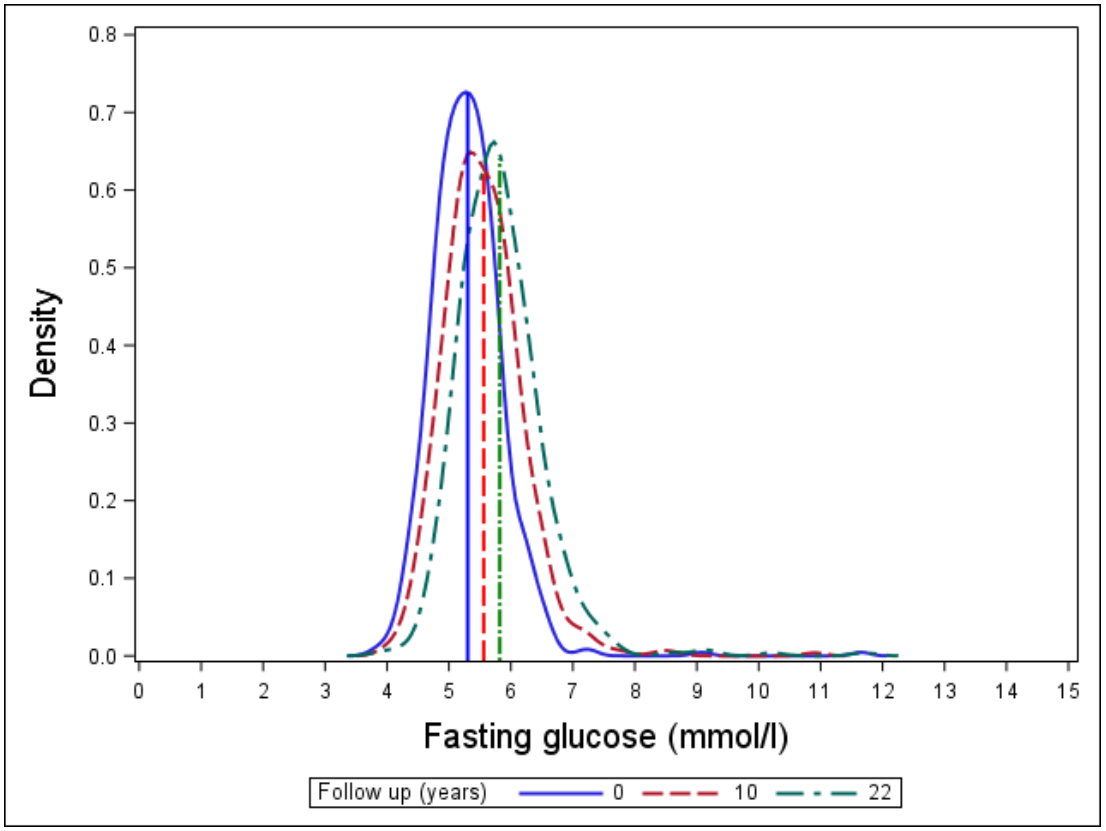
	10-year follow-up					22-year follow-up				
	Participated		Alive and did not participate			Participated		Alive and did not participate		
Baseline variable	N	Mean	N	Mean	p	N	Mean	N	Mean	p
Age (years), women	486	52.5	69	52.3	0.864	354	51.5	152	53.3	0.011
Age (years), men	433	52.2	89	52.4	0.744	273	50.4	127	53.0	0.000
Weight (kg), women	484	69.3	68	72.2	0.091	352	68.9	151	69.5	0.601
Weight (kg), men	433	80.8	89	80.1	0.652	273	80.2	127	80.8	0.641
Height (cm), women	484	162	68	162	0.896	352	162	151	162	0.707
Height (cm), men	432	175	89	175	0.983	272	176	127	175	0.662
BMI (kg/m^2), women	484	26.5	68	27.7	0.050	352	26.3	151	26.6	0.487
BMI (kg/m^2), men	432	26.2	89	26.0	0.621	272	25.9	127	26.2	0.499
Waist (cm), women	482	85.0	66	86.7	0.306	351	84.4	149	85.2	0.457
Waist (cm), men	431	94.0	89	94.5	0.700	271	93.4	127	93.8	0.697
Systolic blood pressure (mmHg), women	483	134	68	137	0.388	352	132	150	138	0.003
Systolic blood pressure (mmHg), men	430	134	88	140	0.003	272	132	127	137	0.003
Diastolic blood pressure (mmHg), women	483	82	68	82	0.680	352	81	150	84	0.019
Diastolic blood pressure (mmHg), men	430	87	88	87	0.607	272	86	127	87	0.857
Fasting glucose (mmol/l), women	473	4.8	65	5.1	0.001	349	4.7	146	4.8	0.278
Fasting glucose (mmol/l), men	419	4.8	83	4.9	0.361	269	4.8	121	4.8	0.895
2h glucose (mmol/l), women	472	5.6	64	5.9	0.227	349	5.5	146	5.8	0.069
2h glucose (mmol/l), men	416	5.3	83	5.5	0.328	268	5.1	120	5.5	0.037
Cholesterol (mmol/l), women	485	5.6	68	5.8	0.225	353	5.5	151	5.7	0.069
Cholesterol (mmol/l), men	430	5.7	89	5.5	0.144	270	5.6	127	5.6	0.745
HDL-cholesterol (mmol/l), women	484	1.6	67	1.6	0.701	351	1.6	151	1.6	0.888
HDL-cholesterol (mmol/l), men	428	1.4	88	1.4	0.601	270	1.3	126	1.4	0.118
LDL-cholesterol (mmol/l), women	480	3.5	65	3.5	0.772	348	3.4	150	3.6	0.173
LDL-cholesterol (mmol/l), men	415	3.7	87	3.5	0.090	260	3.6	125	3.6	0.586
Triglycerides (mmol/l), women	484	1.2	68	1.5	0.001	352	1.2	151	1.2	0.228
Triglycerides (mmol/l), men	430	1.5	88	1.4	0.640	270	1.5	127	1.4	0.270

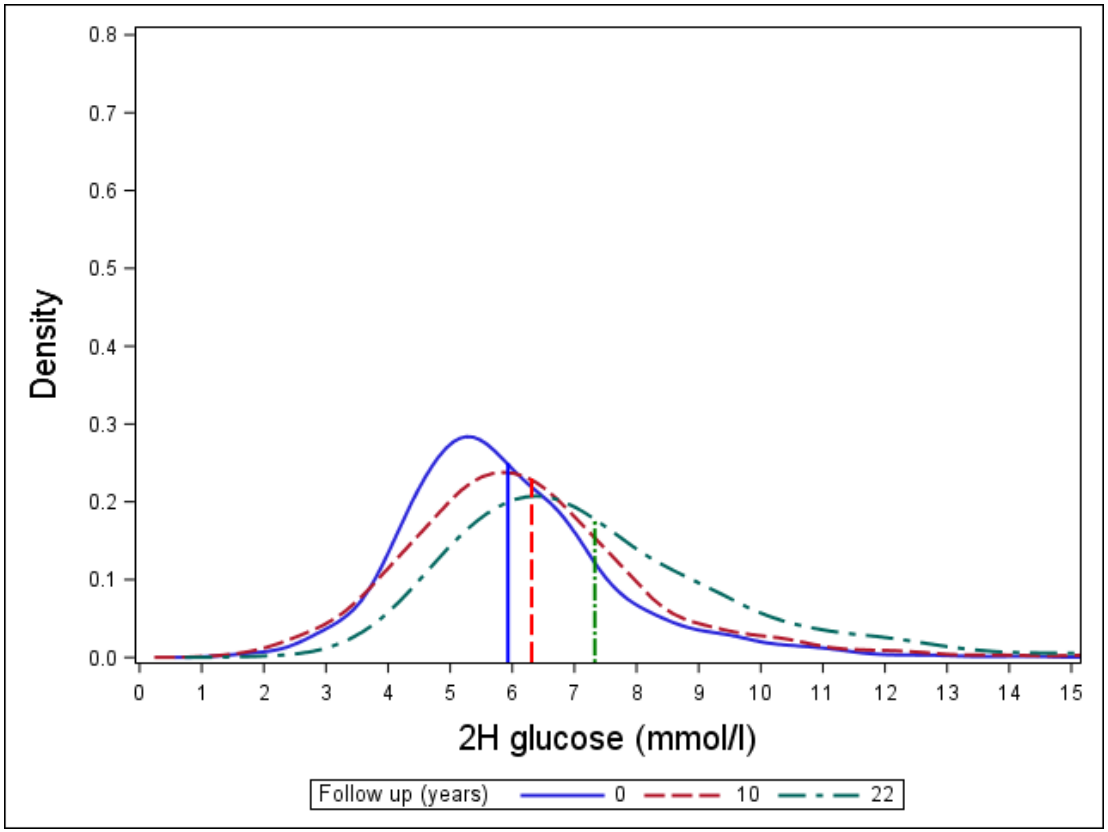
p is significance of t-test when comparing the mean of participants with mean of non-participants.

Supplementary Table 4: Population of Savitaipale by sex and year of birth and survey invitation and participation status at baseline

Number of people living in Savitaipale			**Invited**		**Not participated**		**Participated**					
Birth	men	women	men	women	men	women	men		women		In total	
year	n	n	n	n	n	n	n	%	n	%	n	%
1956	23	29	23	29	12	16	11	47.8	13	44.8	**24**	46.2
1955	30	23	27	23	9	2	18	66.7	21	91.3	**39**	78.0
1954	35	29	35	29	7	7	28	80.0	22	75.9	**50**	78.1
1953	29	33	29	33	8	4	21	72.4	29	87.9	**50**	80.6
1952	28	31	28	31	5	2	23	82.1	29	93.5	**52**	88.1
1951	45	24	45	24	13	3	32	71.1	21	87.5	**53**	76.8
1950	48	19	48	19	13	2	35	72.9	17	89.5	**52**	77.6
1949	49	33	48	33	10	5	38	79.2	28	84.8	**66**	81.5
1948	37	39	37	39	10	4	27	73.0	35	89.7	**62**	81.6
1947	41	36	40	36	9	3	31	77.5	33	91.7	**64**	84.2
1946	28	31	28	31	7	4	21	75.0	27	87.1	**48**	81.4
1945	43	31	43	31	12	7	31	72.1	24	77.4	**55**	74.3
1944	28	33	28	33	9	11	19	67.9	22	66.7	**41**	67.2
1943	29	29	29	29	11	6	18	62.1	23	79.3	**41**	70.7
1942	21	24	21	24	6	3	15	71.4	21	87.5	**36**	80.0
1941	39	38	39	38	13	5	26	66.7	33	86.8	**59**	76.6
1940	22	27	22	27	3	2	19	86.4	25	92.6	**44**	89.8
1939	41	38	41	38	9	8	32	78.0	30	78.9	**62**	78.5
1938	31	25	29	25	7	7	22	75.9	18	72.0	**40**	74.1
1937	28	32	27	32	7	9	20	74.1	23	71.9	**43**	72.9
1936	40	28	39	28	5	3	34	87.2	25	89.3	**59**	88.1
1935	45	25	44	25	7	5	37	84.1	20	80.0	**57**	82.6
1934	37	33	35	33	16	5	19	54.3	28	84.8	**47**	69.1
1933	33	41	15	18	5	4	10	66.7	14	77.8	**24**	72.7
All	**830**	**731**	**800**	**708**	**213**	**127**	**587**	**73.4**	**581**	**82.1**	**1168**	**77.5**

Supplementary Figure 1. Percent (Density) distributions of fasting and two-hour plasma glucose values during the baseline (0), 10-year and 22-year follow-up examination in the study participants who did not use glucose lowering drugs at the time of examination. The whole blood glucose value measured at baseline is converged to plasma glucose by a factor of 1.12. The mean value is marked with a vertical line.


Density
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Fasting glucose (mmol/l)
Follow up (years) 0 10 22


Density
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
2H glucose (mmol/l)
Follow up (years)
0
10
22