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Áhrif efnaskipta- og umhverfisþátta á myndun sykursýki af tegund 2 og breytingar á dánartíðni tengdar sykursýki á tímabilinu frá 1993 til 2004

Lýðgrunduð hóprannsókn byggð á Reykjavíkurrannsókn og Öldrunarrannsókn Hjartaverndar

Elín Ólafsdóttir

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ÁGRIP

Bakgrunnur Algengi sykursýki af tegund 2 (SS2) hefur vaxið ört um heim allan á síðustu áratugum. Þótt munur sé á algengi milli landa og milli heimshluta vegna ólíkra kynstofna, umhverfisþátta og lífsmáta, er þróunin sú sama hvert sem litið er, og hefur verið líkt við alheimsfaraldur. Við skipulagningu á forvörnum og meðferð sjúklinga er greinargóð þekking á faraldsfræði SS2 nauðsynleg heilbrigðisstarfsfólki og yfirvöldum á hverjum stað.

Markmið Að kanna í lýðgrunduðu íslensku þýði áhrif efnaskipta- og umhverfisþátta fyrr á ævinni á áhættu á að fá SS2 síðar á ævinni. Að kanna breytingar á dánartíðni eldri einstaklinga milli áranna 1993 og 2004 og meta tengsl dánartíðni við breytingar í áhættuþáttum hjarta- og æðasjúkdóma, aukinnar læknismeðferðar og SS2 á sama tímabili. Að kanna áhrif kólesteról lækkandi lyfja (statina) á dánartíðni eldri einstaklinga með og án SS2.

Rannsóknarþýðið Lýðgrundað þýði úr Reykjavíkurrannsókn (N=19381; karlar 48%) og Öldrunarrannsókn Hjartaverndar (N=5764; karlar 43%).

Hluti I Af þátttakendum í Reykjavíkurrannsókn Hjartaverndar (áfanga I-V, N=17811) höfðu tveir þriðju hlutar flutt til Reykjavíkur frá sveitum og sjávarsíðu landsins um 20 ára aldurinn en um þriðjungur bjó í Reykjavík frá fæðingu. Metin voru áhrif búsetu í uppvexti á áhættuna á að fá SS2 síðar á ævinni. Hlutfallsleg áhætta á að fá SS2 var 45% lægri í körlum (RR 0.55; 95% CI 0.41-0.74) og 27% lægri í konum (RR 0.72; 95% CI 0.54-0.95) sem bjuggu í sveit fyrstu 20 ár ævinnar miðað við að búa í Reykjavík frá fæðingu. Af þeim sem komu úr sveit var langlægst algengi hjá þeim sem komu frá Austurlandi en hæst frá Suðurlandi. Munurinn á umhverfisþáttum í uppvexti, bæði hvað varðar mataræði og líkamlegt vinnuálag er möguleg skýring á þessum verndandi áhrifum af því að alast upp í sveit. Mismunandi erfðaþættir kunna einnig að hafa áhrif. Tilgáta okkar er sú að umhverfisþættir snemma á ævinni hafi varanleg áhrif á efnaskiptaferla sem í tilviki SS2 eru verndandi við þær aðstæður sem hér er greint frá.

Hluti II Einstaklingum í fyrri hluta Öldrunarrannsóknar Hjartaverndar (N=2251) á aldrinum 65-95 ára, var skipt í þrjá undirhópa eftir SS2 og útkomu úr blóðsykurmælingum. 75% höfðu eðlilega blóðsykurstjórnun, 14% voru með skerta blóðsykurstjórnun og 11% voru með sykursýki af tegund 2. Gildi áhættuþátta sykursýki og hjartasjúkdóma á miðjum aldri (meðalaldur 50 ár) voru könnuð og borin saman við gildin á efri árum (meðalaldur 76 ár) hjá hópunum þremur. Fjölskyldusaga um sykursýki og há gildi líkamsþyngdarstuðuls, þríglyceríða og systolísks blóðþrýstings á miðjum aldri tengdust sykursýki á efri árum. Þessir

þrír áhættuþættir voru áfram hæstir hjá þeim sem greindust með SS2, sem bendir til að greina megi áhættuna á að fá sjúkdóminn og hefja forvarnir löngu áður en sykurbúskapur brenglast.

Hluti III Algengi SS2 í síðasta áfanga (VI) Reykjavíkurrannsóknarinnar 1993 (N=1506) var sama og greindist í Öldrunarrannsókninni 2004 (N=4814) eða 12%, aldursbil í báðum rannsóknahópum var 70-87 ár. Milli 1993 og 2004 varð 32% lækkun á dánartíðni af völdum hjarta- og æðasjúkdóma og 19% vegna allra orsaka í rannsóknarhópunum. Lækkun á dánartíðni varð meiri í hópi sykursjúkra eins og sést þegar aðlöguð áhættuhlutföll milli þeirra sem voru með sykursýki og annarra voru skoðuð, en þau mældust 1,88 (95% CI 1,24-2,85) árið 1993 og lækkuðu í 1,46 (95% CI 1,11-1,91) 2004. Á sama tíma lækkuðu gildi á helstu áhættuþáttum hjart- og æðasjúkdóma, bæði meðal þeirra sem voru með SS2 og annarra. Árið 2004 fékk hærra hlutfall einstaklinga með sykursýki sykurlækkandi lyf, háþrýstingslyf og blóðfitulækkandi lyf heldur en árið 1993. Lækkun á dánartíðni af völdum hjarta- og æðasjúkdóma og af öllum orsökum má skýra að hluta vegna lækkunar á áhættuþáttum á þessu tímabili en að hluta vegna aukinnar læknismeðferðar. Sykursýki af tegund 2 reyndist þó enn óháður áhættuþáttur hjarta- og æðasjúkdóma.

Hluti IV Í Öldrunarrannsókninni (N=5152, aldursbil 66-96 ár) var dánartíðni af völdum hjarta- og æðasjúkdóma hjá einstaklingum með SS2 50% (95% CI 8-72%) lægri hjá þeim sem notuðu statin lyf og dánartíðni af öllum orsökum 53% (29-68%) lægri. Þessi lækkun var óháð því hvort þeir voru með hjarta- og æðasjúkdóm eða voru á sykurlækkandi lyfjum. Meðal þeirra sem ekki voru með SS2 var dánartíðni af völdum hjarta- og æðasjúkdóma 16% (-24-43%) lægri og dánartíðni af öllum orsökum 30% (11-46%) lægri í hópnum sem notaði statin. Rannsóknin bendir til þess að notkun statina sé æskilegur þáttur í fjöllyfjameðferð við SS2.

Ályktanir Niðurstöður okkar styðja þá tilgátu að lífsskilyrði frá unga aldri og fram eftir ævi verndi gegn myndun SS2 á síðari æviárum. Frá 1993 til 2004 lækkaði dánartíðni af völdum hjarta- og æðasjúkdóma samfara lækkun á áhættuþáttum þessa sjúkdómaflokks meðal þjóðarinnar. Bætt læknisþjónusta kann einnig að hafa átt sinn þátt í að dregið hefur úr dauðsföllum, jafnt meðal einstaklinga með SS2 og annarra. Þar sem SS2 reyndist óháður áhættuþáttur hjarta- og æðasjúkdóma og algengi SS2 eykst í yngri aldurshópum er mikilvægt að vinna áfram að forvörnum og mati á viðeigandi læknismeðferð.

Lykilorð: Hóprannsókn, sykursýki af tegund 2, aldraðir, Reykjavíkurrannsókn Hjartaverndar, Öldrunarrannsókn Hjartaverndar

ABSTRACT

Background The global prevalence of type 2 diabetes (T2D) has increased dramatically in the last decades. Although incidence and prevalence varies in different parts of the world because of diverse genetic, environmental and lifestyle factors, the trend is the same world wide and has for some time been characterized as an epidemic. Detailed local information on the epidemiology of T2D is essential for health care providers when planning prevention, patient care and control of the micro- and macro-vascular complications of diabetes.

Aims To analyse the metabolic and environmental conditions earlier in life leading to the onset of T2D later in life. To estimate the secular trend in mortality risk in older persons between the years 1993 and 2004 associated with changes in cardiovascular risk factors, medical treatment and type 2 diabetes. To assess the use of statins on mortality rate in persons with and without type 2 diabetes.

Study population The population-based Reykjavik Study (N=19381; men 48%) and the Age, Gene/ Environment Susceptibility (AGES)-Reykjavik Study (N=5764; men 43%).

Study I Of 17811 participants in the Reykjavik Study (stages I-V) that lived in Reykjavik and surrounding area in 1967, two thirds had moved from a rural or coastal area to the capital after the age of 20, allowing a comparison of early environment on the risk of developing T2D later in life. The relative risk of developing T2D was 45% lower in men (RR 0.55; 95% CI 0.41-0.74) and 27% lower in women (RR 0.72; 95% CI 0.54-0.95) that lived in a rural area for the first 20 years of their life compared with urban dwellers from birth. Difference in environmental conditions while growing up, both as relates to nutrition and the vigour of physical work, is the most likely reason for this protective effect of the rural environment. Genetic factors may also play a part. We postulate a prolonged effect of early development on glucose metabolism and risk of developing T2D.

Study II A cohort of 2251 persons (AGES-Interim), aged 65-95 years, was split into three groups based on glucometabolic status: 75% were normoglycemic, 14% had impaired fasting glucose, and 11% had type 2 diabetes. The levels of diabetic risk parameters in midlife (mean age 50y) were compared to levels in late life (mean age 76y) in the three study groups. Family history and higher levels of BMI, triglycerides and systolic blood pressure in midlife were associated with the development of T2D in late life, suggesting risk can be evaluated long before the onset of diabetes. Risk factors levels increased in all study groups but the T2D group remained highest also in late life, allowing a scope for more aggressive measures in preventing or delaying development of T2D and its impact on cardiovascular health.

Study III Prevalence of T2D in the last stage of the Reykjavik Study (stage VI, N=1506) in 1993 was equivalent to that in the AGES-Reykjavik cohort (N=4814) in 2004 or 12%, age range in both cohorts 70-87y. A 32% decline in cardiovascular mortality and 19% in all-cause mortality rates was observed between 1993 and 2004. The decline was greater in persons with T2D as illustrated by the decline in adjusted hazard ratio of cardiovascular mortality in individuals with diabetes compared to those without, from 1.88 (95% CI 1.24-2.85) in 1993 to 1.46 (95% CI 1.11-1.91) in 2004. Concurrently we observed a decrease in major cardiovascular risk factors both in those with and without diabetes along with a higher proportion of persons with diabetes receiving glucose-lowering, hypertensive and lipid-lowering medication in 2004. This reduction in cardiovascular and all-cause mortality rate might be explained partly by improved cardiovascular risk factor profiles and medical treatment between the years 1993 and 2004. T2D, however, still persisted as an independent risk factor for cardiovascular mortality.

Study IV In the AGES study (N=5152, age range 66-96y) statin use was associated with a 50% (95% CI 8-72%) lower cardiovascular mortality and 53% (29-68%) lower all-cause mortality rates in persons with type 2 diabetes. For those without diabetes, statin use was associated with a 16% (-24-43%) lower cardiovascular and 30% (11-46%) lower all-cause mortality rates. The main finding was that statin medication markedly reduced the excess cardiovascular and all-cause mortality risk, irrespective of the presence or absence of coronary heart disease or glucose-lowering medication. Our study suggests that treatment with statins is paramount in the multifaceted management of T2D.

Conclusions Our data support the hypothesis that environmental and metabolic conditions from an early age protect against the development of T2D later in life. Over the period from1993 to 2004 cardiovascular mortality rate in older persons with and without T2D diminished in parallel with reduction of cardiovascular risk factors in the population at large. Improved medical treatment may also have reduced the excess mortality rate seen in persons with T2D as shown in study IV. T2D, however, still persisted as an independent risk factor for cardiovascular mortality and as prevalence of T2D is on the rise in the younger age groups in Iceland enforcement in primary as well as secondary prevention is urgently called for.

Key words Cohort study, type 2 diabetes, older persons, Reykjavik Study, AGES-Reykjavik

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CONTENTS

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AGES-Reykjavik	Age, Gene/Environment Susceptibility - Reykjavik Study
BMI	body mass index
CE	coronary events
CHD (chd)	coronary heart disease
CI	confidence interval
CRP	C-reactive protein
CVD	cardiovascular disease
ECG	electrocardiograph
GT	glucose tolerance
HbA_{1c}	haemoglobin A_{1c}
HDL	high density lipoproteins
$HOMA_{IR}$	homeostasis model assessment: insulin resistance
HR	hazard ratio
IDDM	insulin-dependent diabetes mellitus
IDF	International Diabetes Federation
IFG	impaired fasting glycaemia
IGT	impaired glucose tolerance
LDL	low density lipoproteins
MI	myocardial infarction
MS	metabolic syndrome
N (n)	number
NCEP	National Cholesterol Education Program
NDDG	National Diabetes Data Group
NHANES	National Health and Nutrition Examination Survey
NIDDM	non-insulin-dependent diabetes mellitus
RS	Reykjavik Study
SS2	sykursýki af tegund 2
T2D	type 2 diabetes

T2DM	type 2 diabetes mellitus
dT2DM	diagnosed type 2 diabetes mellitus
uT2DM	undiagnosed type 2 diabetes mellitus
TG	triglycerides
VLDL	very low density lipoproteins
WHO	World Health Organization

LIST OF FIGURES

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LIST OF PAPERS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-IV):

I. **Elin Olafsdottir**, Johanna E. Torfadottir, Laufey Steingrimsdottir, Gunnar Sigurdsson, Bolli Þorsson, Rafn Benediktsson, Gudny Eiriksdottir, Thor Aspelund, Unnur A. Valdimarsdottir, Vilmundur Gudnason. Rural residency in early life associated with reduced risk of developing type 2 diabetes: the population-based Reykjavik Study. [Manuscript].

II. **Elin Olafsdottir**, Thor Aspelund, Gunnar Sigurdsson, Bolli Thorsson, Rafn Benediktsson, Tamara B. Harris, Lenore J. Launer, Gudny Eiriksdottir, Vilmundur Gudnason (2009). Unfavourable risk factors for type 2 diabetes mellitus are already apparent more than a decade before onset in a population-based study of older persons: the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik). *Eur J Epidemiol. 24(6),* 307-14.

III. **Elin Olafsdottir**, Thor Aspelund, Gunnar Sigurdsson, Bolli Thorsson, Rafn Benediktsson, Tamara B. Harris, Lenore J. Launer, Gudny Eiriksdottir, Vilmundur Gudnason. Secular trend in mortality risk associated with type 2 diabetes in older persons between 1991 and 2006: the population-based Reykjavik and AGES-Reykjavik studies. [Manuscript submitted].

IV. **Elin Olafsdottir**, Thor Aspelund, Gunnar Sigurdsson, Bolli Thorsson, Rafn Benediktsson, Tamara B. Harris, Lenore J. Launer, Gudny Eiriksdottir, Vilmundur Gudnason (2011). Effects of statin medication on mortality risk associated with type 2 diabetes in older persons: the population-based Age, Gene/Environment Susceptibility-Reykjavik Study. *BMJ Open. Jan 1;1(1),* e000132. Epub 2011 Jun 29.

Papers II and IV are reprinted by kind permission of the publishers. The papers or manuscripts do not appear in the on-line version of this thesis.

DECLARATION OF CONTRIBUTION

Vilmundur Gudnason had access to all the data and takes full responsibility for the content of the work presented. Drafting of the manuscript: Elin Olafsdottir drafted the manuscripts and the papers already published. Thor Aspelund and Vilmundur Gudnason added constructive work in finalising the manuscripts and Rafn Benediktsson also helped with finalising paper IV. Statistical analyses were in the hands of Elin Olafsdottir and Thor Aspelund. Data collection and preparation: Elin Olafsdottir, Thor Aspelund, Vilmundur Gudnason, Bolli Thorsson, Gudny Eiriksdottir, Gunnar Sigurdsson, Lenore Launer and Tamara Harris. All authors contributed to the interpretation of the results, read and commented on the manuscripts and approved the final versions. In paper I Johanna E. Torfadottir contributed to the statistical analysis and along with Laufey Steingrimsdottir and Unnur A. Valdimarsdottir and the other co-authors commented on the manuscript and approved the final version.

1 INTRODUCTION

The global prevalence of type 2 diabetes has increased dramatically worldwide in the last decades (Lam & Leroith, 2012; Zimmet et al., 2001) and the same development has been observed in Iceland (Thorsson et al., 2009). Although incidence varies in different parts of the world because of different genetic, environmental and lifestyle factors, the trend is the same worldwide and has for some time been characterized as an epidemic (Zimmet, 2000). Detailed local information on the epidemiology of type 2 diabetes is essential for health care providers when planning prevention, care and control of both micro- and macro vascular complications of the disease. The overall aim of the present work was to investigate the effect of metabolic and environmental conditions on the development of type 2 diabetes in Iceland and look at the secular trend in medical treatment and mortality risk associated with type 2 diabetes in older persons, between the years 1993 and 2004. The study is based on data from the population-based Reykjavik Study and the Age, Gene/Environment Susceptibility-Reykjavik Study.

1.1 Early history of diabetes and the discovery of insulin

Although diabetes has been known for centuries the term diabetes mellitus, relating to the honeyed taste of urine, was first used in the late 18th century by the Scottish born army surgeon-general John Rollo, when he published his *"account of two cases of diabetes mellitus with remarks as they arose during the progress of the cure"* in 1797 (Rollo, 1797).

The 19th century French physiologist Claude Bernard (Bernard, 1853) contributed greatly to the understanding of diabetes and glucose metabolism, when he discovered the glycogenic function of the liver. He concluded from his studies that the liver, in addition to secreting bile, was *"the seat of an internal secretion, by which it prepared sugar at the expense of the elements of the blood passing through it"*. In 1869 the German pathologist Paul Langerhans was the first to describe the pancreatic islets, named after him, when they were shown to produce a glucose lowering substance (Sakula, 1988), and later the Belgian scientist Jean de Meyer named the glucose lowering substance of the pancreas, insulin, after the islets of Langerhans (Bliss, 2007). Finally the major breakthrough in diabetic research came when insulin was purified in 1921 and successfully used in treating a diabetic patient in Canada,

after a strained but fruitful cooperation of J.J.R. Macleod, Charles Best, Frederick Banting, and James Collip (Hudson, 1979; Raju, 2006).

The first mention of diabetes in Iceland is in a doctoral thesis from 1874, where J. Finsen recorded his experience as a doctor in northern Iceland and concludes *"the disease must be very rare"* as he had not seen a single case of diabetes during a 10 year period between 1856-66 (Finsen, 1874). At the turn of the century in reports of Public Health in Iceland, 1901-1904, the same opinion on the rarity of diabetes in Iceland is expressed as only 4 patients with diabetes were reported over that period (Jonsson, 1941). Again in 1938 the Chief Medical Officer of Iceland, V. Jónsson, stated: *"Diabetes is a very rare disease in Iceland, and it is an extraordinary occurrence for doctors to come across it"* (Jonsson, 1939).

An account on the prevalence of diabetes in Iceland first appeared in 1953, when V. Albertsson recorded his studies on diabetes over the period from 1930 until 1952 (Albertsson, 1953). Albertsson based his research on records from his own clinical practice in endocrinology, questionnaires sent to other physicians in the country, and the study of national death certificates. He observed a steady increase in prevalence of diabetes over the study period. The method of diagnosis was either urine glucose measurements, blood glucose measurements after a full meal, or a modified glucose tolerance test. In 1930 he reported the prevalence of diabetes at all ages to be 0.03% but in 1952 it had risen to 0.1%.

In 1992 the Ministry of Health published a report on diabetes in Iceland, as a response to the St. Vincent declaration from 1989. The report contains a good overview on the status of type 1 diabetes, gestational diabetes and on diabetic complications at that time (Thorsson et al., 1992).

The Reykjavik Study, conducted by the Icelandic Heart Association, was the first large survey where the prevalence of type 2 diabetes in Iceland was estimated and showed an overall age-standardized prevalence of 2.7% for men and 2.0% for women in the age group 34-79 years (Vilbergsson et al., 1997). Further data from the Icelandic Heart Association have shown a steady increase in prevalence of type 2 diabetes from 1967 to 2007, when the prevalence rose from 3% to 6% in men and from 2% to 3% in women in the age group 45-64 years (Bergsveinsson et al., 2007; Thorsson et al., 2009). The prevalence of type 2 diabetes, however, is still lower in Iceland than in most of our neighbouring countries.

1.2 Diagnosis and classification of diabetes

Research, management and prevention of both type 1 and type 2 diabetes depends on an appropriate and contemporary classification of the disease. Through the years the World Health Organization (WHO) has published several recommendations on the classification and diagnostic criteria of diabetes. The first recommendation published in 1965 (WHO, 1965) created some confusion and after the National Diabetes Data Group (NDDG) formulated a classification of diabetes in 1979, the WHO Expert Committee reviewed, amended and adopted the NDDG recommendations in a second report in 1980 and again in a modified form in 1985 (WHO, 1985). The 1980 Expert Committee proposed two major classes of diabetes and named them insulin-dependent diabetes mellitus (IDDM) or type 1 and non-insulin-dependent diabetes mellitus (NIDDM) or type 2. Both the American Diabetes Association (ADA) and WHO have now eliminated the terms IDDM and NIDDM on the basis that these terms have been confusing and frequently lead to misclassification. The terms type 1 and type 2 are retained as people with any type of diabetes may require insulin treatment at some stage of their disease. The type 1 diabetes includes those cases attributable to an autoimmune process, as well as those with beta-cell destruction, while type 2 includes the common major form of diabetes, which results from defects in insulin secretion, with a major contribution from insulin resistance (either predominantly insulin resistance with relative insulin deficiency or predominantly an insulin secretory defect with/without insulin resistance).

The WHO reviewed their recommendations on diabetes criteria in 1999 (WHO, 1999) and again jointly with the International Diabetes Federation in November 2005 (WHO/IDF, 2006), where it was recommended that the WHO diagnostic criteria from 1999 should be maintained. Correct classification and phenotyping is important to ensure correct interpretation and comparability of different studies, and the WHO criteria from 1999 are followed in the current thesis, using a single measurement of fasting blood glucose of ≥ 7.0 mmol/L or higher for diagnoses of type 2 diabetes, in addition to history of diabetes and diabetic medication, and ≥ 6.1 and < 7.0 mmol/L for impaired fasting glycaemia. The majority of epidemiological studies use a single measurement of fasting blood glucose for screening purposes although it is considered more reliable to use a mean of two measurements done two weeks apart. If a second fasting glucose level is used to confirm the diagnosis of type 2 diabetes (American Diabetes Association guidelines) 70% repeatability may be expected (Selvin et al., 2007). After an extensive review of both established and emerging epidemiological evidence, an International Expert Committee recommended the use of

HbA1c test to diagnose diabetes (Nathan, 2009). The diagnostic test should be performed using certified methods that are traceable to International Federation of Clinical Chemistry reference method.

An overview of the WHO recommendations from 1999 on levels of blood glucose for diagnosis of diabetes mellitus and other categories of hyperglycaemia is shown in Table 1 below (WHO, 1999).

Table 1. Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia

Diagnosis	*Blood glucose:*	*Serum/plasma, mmol/l:*
Diabetes	Fasting	≥ 7.0
	or 2-hr glucose tolerance (GT)*	≥ 11.1
Impaired glucose tolerance (IGT)	Fasting	< 7.0
	and 2-hr GT*	≥ 7.8 and < 11.1
Impaired fasting glycaemia (IFG):	Fasting	≥ 6.1 and < 7.0
	and if measured 2-hr GT*	< 7.8

* after a 75 g oral glucose load

Insulin resistance, with concomitant lipid and thrombotic abnormalities, is also a characteristic feature of type 2 diabetes and along with conventional atherosclerotic risk factors, determines the risk for cardiovascular disease. The rise in prevalence of type 2 diabetes in the last 20-30 years has stimulated research not only in epidemiology, but also in genetic, environmental, and behavioural factors contributing to the epidemic. Although hyperglycaemia is usually the first abnormality to be observed in type 2 diabetes it is the macro- and micro-vascular complications that are detrimental to health of the people suffering from the disease, and at time of diagnosis they are usually already in progress.

1.3 Development of type 2 diabetes

In the development of type 2 diabetes insulin resistance and β-cell dysfunction both precede measured defect in glucose tolerance and occur long before pre-diabetes is discovered. One has not been shown to precede or cause the other. Type 2 diabetes can thus be seen as a “dual-defect disease” with both defects of equal importance. A genetic predisposition seems to be

mandatory and several genetic variants have been discovered affecting both β-cell dysfunction and insulin resistance (Leahy, 2008; Saxena et al., 2012; Wheeler & Barroso, 2011). The phenotype of type 2 diabetes is also influenced by many environmental factors that put a stress on the glucose homeostasis system, possibly through some epigenetic mechanisms.

Familial trend of type 2 diabetes has been recognised for a long time and was shown clearly in the studies on identical twins where Barnett and co-workers hypothesised that type 2 diabetes was predominantly, even perhaps entirely inherited (Barnett et al., 1981a; Barnett et al., 1981b). The cumulative prevalence of diabetes at the age of 80 is about 3.5 times higher in people with first degree relatives with type 2 diabetes compared to persons without any affected relative (Valdez, 2009). A family history of type 2 diabetes has therefore often been included in the variety of tools designed to detect either people at risk of developing type 2 diabetes or people with undiagnosed diabetes. More recently genome-wide association studies have uncovered dozens of common genetic variants associated with risk for type 2 diabetes (Wheeler & Barroso, 2011) and obesity (Billings & Florez, 2010; Strawbridge et al., 2011), but this new information has had little influence as yet on the clinical management of diabetes or obesity.

In his review article McCarthy points to several reasons for this (McCarthy, 2010). One reason is the modest effect size of the variants, also the challenge of determining molecular effects of "noncoding" variants (i.e., variants that affect gene regulation rather than amino-acid sequence of a protein), and the difficulty of telling which transcript(s) within a locus mediate the effects on disease risk.

Several areas must be developed to realize the potential influence of genetic information on disease risk, such as characterizing disease mechanisms accessible to treatment or prevention, improving processes of risk prediction and diagnosis, and developing individualised approaches to treatment and prevention. In discussing disease mechanisms, McCarthy mentions the "cluster of traits referred to as the metabolic syndrome" and observes that little or no genetic evidence supports the existence of such a "pathophysiological entity." He continues that we haven't been very successful at finding variants influencing the metabolic syndrome as a whole and "that may be because the variants are there and we didn't find them yet, or the metabolic syndrome has more to do with environment and aging (perhaps via epigenetics) than with genetic variation."

Rapid advances in the field of epigenetics have been revealing a molecular basis for how heritable information other than DNA sequence can influence gene function (Bird, 2007). These advances add to our understanding of how transcriptional regulation, nuclear organization, development and disease can be modified by environmental stimuli. In their review article Fradin and Bougneres conclude that epigenetic programming may be important at two levels (Fradin & Bougneres, 2011). Both in the metabolic tissues, including the β-cells, liver, muscle and adipose tissue, where epigenetic events can allow persistent and time-dependent changes in gene expression potential, but also in the brain where epigenetics can be used for the integrated modulation of metabolism and feeding behaviours in response to multiple environmental cues.

1.4 Environmental factors affecting the development of type 2 diabetes in Iceland

Until around 1900 the inhabitants of Iceland were primarily engaged in food production in one way or another (Jonsson, 1998) and the most important feature of the Icelandic diet was the predominance of animal-based foods to such an extent that it had few parallels in Europe, except perhaps among the Inuit in Greenland, the nomads in Lapland and coastal communities in the far north of Europe. This changed slowly and by 1910 grain-based foods were providing more than half of the total energy value in the Icelandic diet, which we can take as a turning point in the transition from animal-based to grain-based diet.

In Iceland the industrial age started in the early 20th century with the first hydroelectric power plant being built in 1904 and the acquisition of the first steam trawler in 1905. A second burst of modern technology came with the Second World War and was eagerly adopted causing a social change that has continued since at an ever escalating pace. Before 1940 machinery in farming was primitive, roads were poor and horses still widely used on farms and in transportation. In Reykjavik cars were uncommon; people would walk and carry their domestic supplies. People in general were accustomed to working hard for long hours, both men and women, even children, at least in rural areas, and few were overfed.

In his overview on "Changes in food consumption in Iceland 1770-1940," G. Jónsson gives a good insight into the national food consumption from 1900 to 1940, calculated from food supply data (Jonsson, 1998). The food supply data show a decrease in the average energy intake at the end of the First World War and again in the 1930s which corresponds well with setbacks in the economy at those times.

The first comprehensive dietary survey in Iceland, initiated by the newly established Nutrition Council, was carried out in 1939-1940. The professor of public health, Júlíus Sigurjónsson, was appointed to direct the work. Households were selected in rural areas and coastal villages around the country as well as from urban Reykjavik and food consumption of the families recorded over a 12 month period. The results from the dietary survey along with information on general health, housing and sanitary conditions was published in a report in 1943 (Sigurjonsson, 1943). A short overview of the average male consumption from that report is shown in Table 2 below.

Table 2. An average food consumption by males living in different areas 1939-40

	milk products cal/d	**grain** cal/d	**fish** g/d	**meat** g/d	**potatos** g/d	**animal products** % of cal/d	**total calorie intake**
Rural areas	1126	927	140	177	247	58	3553
Coastal areas	649	1068	354	106	233	45	3311
Urban Reykjavik	653	771	213	133	216	46	2829

Although living conditions were harsh in many places at the time of this survey, food supply was adequate in most households. The main conclusion was, however, that calcium intake was too low in many of the households in coastal villages and in several places vitamin C and D intake was too low. Compared to food intake in neighbouring countries less calories came from grain and much higher percentage from animal sources, especially in the rural areas at this time.

The difference in total calorie intake between rural and urban areas is similar to what was seen in other countries at the time. The difference in calorie intake reflects most likely the difference in heavy manual labour men in the rural areas and coastal villages were subjected to, thus requiring more food intake.

1.5 Consequences of type 2 diabetes

The pathological processes involved in the detrimental effect of diabetes include haemodynamic and metabolic abnormalities such as endothelial dysfunction, inflammation, vasoconstriction, oxidation and fibrosis. These may be due in part to hypertension that coexists in about 90% of older diabetic patients. It is clear that there is a distinct pro-inflammatory and pro-fibrotic state in diabetes and statins are known to effect these pathways (Martin et al., 2009).

Today, type 2 diabetes is recognised as a group of disorders characterized by hyperglycaemia, associated with microvascular (retinal, renal), macrovascular (coronary, peripheral vascular), and neuropathic (autonomic, peripheral) complications. Over the past 30 to 40 years, accumulated evidence shows that both numerous and etiologically different mechanisms may play a role in the pathogenesis, the clinical course and the emergence of complications of the "diabetic state".

Lipoproteins play a central role in atherosclerosis, the leading cause of death in patients with diabetes. The dyslipidemia in diabetes is characterized by high plasma triglycerides, low levels of HDL-cholesterol and small, dense LDL. The dyslipidemia results from hepatic overproduction of very low density lipoproteins (VLDL), stimulated by the flux of fatty acids from adipose tissues to the liver, raising the levels of VLDL in plasma. As lipoprotein lipase activity is reduced in the diabetic or insulin resistant state the recycling rate of fatty acids back to adipose tissues is slowed down resulting in raised levels of VLDL, free fatty acids and triglyceride levels in plasma (Ginsberg, 2000; Krauss, 2004).

Most of the VLDL in diabetic or insulin resistant persons contains a higher proportion of triglycerides than average VLDL. The large VLDL particles then undergoes an extensive lipolytic process to become small dense LDL (Packard, 1999). Epidemiological data suggests that small dense LDL are more atherogenic than large LDL, with lower levels of antioxidants per particle, increased permeation of arterial endothelium, and prolonged particle residence in plasma with accumulation of lipid peroxides (Krauss, 2004; Packard, 2003).

The increased understanding of the pathophysiology of diabetic dyslipidemia (Taskinen, 2003; Verges, 2010) has led to increased awareness of the importance of treating these disturbances in diabetic patients. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases from the European Society of Cardiology and of the European Association for the Study of Diabetes address the issue (Ryden et al., 2007) and more recently the guidance for the management of elevated triglyceride-rich lipoproteins in patients with cardiovascular

disease and diabetes from the European Atherosclerotic Society discuss in detail how to deal with hypertriglyceridemia (Chapman et al., 2011) in light of the most resent bio-medical information available.

1.6 Epidemiology of type 2 diabetes

In "Epidemiology of Diabetes and its Vascular Lesions," K. West gives a critical review of over 2000 publications on the subject (West, 1978). In his introduction he says "…*diabetes mellitus has become one of the most important of human problems. It is a significant cause of disease and death in all countries and all major races*…". Twenty years later Ekoé, Zimmet and Williams edited "The Epidemiology of Diabetes Mellitus - An International Perspective" with the main aim to disseminate the most recent epidemiological data about diabetes mellitus and provide the current evidence for primary prevention of type 2 diabetes (Ekoe et al., 2001). Meanwhile the prevalence of type 2 diabetes continues to rise world-wide, most likely as a result of an aging population living an increasingly sedentary lifestyle, and consuming foods too high in fat and refined carbohydrates. This rise has not yet reached its maximum as illustrated in numerous population based studies over the last 20 years. As a result type 2 diabetes has become the most costly and burdensome chronic disease of our time and WHO has predicted the global prevalence of diabetes in adults will reach 6.4% in 2030, representing a 39% increase from the year 2000 to 2030. These projections are likely to be underestimated as can been seen from the present trend in many countries. Important overviews on the global prevalence and development of diabetes are illustrated in the Diabetes Atlas [http://www.worlddiabetesfoundation.org/composite-58.htm] as well as the ethnic differences in prevalence of type 2 diabetes. Within Europe the prevalence of diabetes varies considerably and the 2009 estimates from a few of the neighbouring countries taken from the Diabetes Atlas are shown in Table 3 below. The figures include both type 1 and type 2 diabetes in the age group 20-79 years. In most of the listed countries about 90-95% of cases are classified as type 2 diabetes.

Table 3. The estimated % prevalence of diabetes in Iceland and selected neighbouring countries in the age group 20-79 years. From the Diabetes Atlas 2009. (http://www.idf.org/diabetesatlas/downloads)

Country	% prevalence
Iceland	2.07
Norway	4.74
England	4.86
Sweden	7.32
Denmark	7.72
Netherlands	7.72
Finland	8.27
Canada	11.59
Germany	11.96
United States of America	12.34

As individual studies on prevalence of diabetes often use different methodology both in the diagnosis of diabetes and the statistical methods applied, direct comparisons between countries or even areas within countries need to be treated with caution, unless the methodology is standardised. In a recent study from Germany marked regional differences were seen in the prevalence of known type 2 diabetes, at the age 45-74 years and directly standardised to the German population in December 2007 (Schipf et al., 2012). The regional standardised prevalence was highest in the eastern part of Germany (12.0%) and lowest in the south (5.8%) and the estimated national prevalence was 8.2%. Studies from both southern and eastern Europe show a much higher prevalence there than in northern Europe, with data from Spain indicating a prevalence of 10.3% in the age group 30-89 years (Castell et al., 1999) and from Poland a study reported a prevalence of over 15% (Lopatynski et al., 2001). The prevalence in ethnic groups originating from outside Europe often differs significantly from people of white European origin after they adopt the local life style. In Coventry in England the prevalence of type 2 diabetes was 3.2% and 4.7% in men and women of European origin, compared to 12.4% and 11.2% in Asian men and women (Simmons et al., 1991).

In Canada the age and sex adjusted prevalence of type 2 diabetes in persons 20 years and older was 8.8% in 2005 (Lipscombe & Hux, 2007). In the US 2005-2006 the age and sex standardised prevalence of diabetes in adults 20 years and older was 11.0% for non-Hispanic white, 18.7% for non-Hispanic black and 20.1% for Mexican American populations (Cowie et al., 2009). The Native American populations have by far the highest risk of developing type 2

diabetes, with the highest prevalence in the world being reported in the Pima Indians in Arizona, where the prevalence reaches 50% in middle-aged adults (Knowler et al., 1978).

Registration of patients with diabetes at a population level is relatively recent but opens up new possibilities for long-term population based epidemiological studies (Carstensen et al., 2008; Evans et al., 2007). Information on the prevalence of diagnosed type 2 diabetes is now available from the nationwide registration of diabetic patients that was started in Sweden over 15 years ago (Eliasson et al., 2005; Gudbjornsdottir et al., 2009) and is currently also being done in Denmark (Carstensen & Borch-Johnsen, 2011; Carstensen et al., 2011), Finland (Saaristo et al., 2007), Scotland (Barnett et al., 2010) and Canada (Lipscombe & Hux, 2007). These registers open a new era in diabetic research with more detailed information on clinical course of the disease. In other countries changes in prevalence of type 2 diabetes and its association with risk factors will, however, continue to be best approached through population based cohort studies. In Iceland there is no diabetes register.

Epidemiological research has focused on studying risk factors in the hope that by identifying and managing modifiable risk factors, the disease can be prevented, or onset delayed. Obesity has been implicated in the development of diabetes associated with insulin resistance and disturbances in lipid metabolism (Eckel et al., 2011) which precede any detectable imbalance in carbohydrate metabolism.

Cardiovascular disease causes much of the morbidity and mortality associated with type 2 diabetes (Gaede et al., 2003), and modifiable cardiovascular risk factors are therefore included in most studies on diabetes (Gudbjornsdottir et al., 2011). Among the conventional modifiable cardiovascular risk factors are hypertension, high levels of plasma triglycerides and low HDL-cholesterol, smoking and sedentary lifestyle along with several socioeconomic factors.

A search for novel risk factors for type 2 diabetes has also been a focus of research in recent years. In their review on the subject Sattar and co-workers (Sattar et al., 2008) illustrate how many of the novel biomarkers reflect processes related to insulin action or insulin resistance, mediated through the location and function of fat, or via related inflammation or endothelial dysfunction. Their conclusion was that use of these novel biomarkers in helping to identify persons at elevated risk of type 2 diabetes is very much in its infancy. As yet they do not significantly improve risk prediction for future diabetes beyond the simple risk factors that are currently easily available from history, simple examination measures and blood tests.

1.7 Life expectancy and mortality risk of people with type 2 diabetes

Life expectancy has increased in the Western World in the last decades with decline in mortality risk both from cardiovascular disease and from all causes (Bjorck et al., 2009; Kesteloot et al., 2006; Tunstall-Pedoe et al., 1999). This decline in mortality has been attributed to a great extent to the decrease in cardiovascular mortality rate which has been caused by a drop in cardiovascular risk factors and to a lesser degree improved medical treatment. In the INTERHEART study Yusuf and collaborators (Yusuf et al., 2004) showed that nine easily measured and potentially modifiable risk factors account for an overwhelmingly large (over 90%) proportion of the risk of an initial acute myocardial infarction. The validated IMPACT coronary heart disease mortality model (Capewell et al., 1999) has been used to estimate the impact of risk factor reduction and medical treatment on coronary heart disease mortality in several countries (Bots & Grobbee, 1996; Capewell et al., 2000; Ford et al., 2007; Laatikainen et al., 2005; Unal et al., 2005). Between 1981 and 2006 coronary heart disease mortality rates Iceland the decreased by 80% in men and women aged 25 to 74 years, and using this model (Aspelund et al., 2010) 73% of the mortality decrease was attributable to risk factor reductions and approximately 25% of the mortality decrease was attributable to treatments in individuals.

Several studies have suggested that life expectancy of people with type 2 diabetes has improved in recent years relative to those without diabetes (Eliasson et al., 2008; Gregg et al., 2007; Gulliford & Charlton, 2009; Lutgers et al., 2009; Thomas et al., 2003). An 8 year follow up of two large population-based studies in Norway, the Hunt study I and II shows a general reduction in mortality rates over a 10 year period between 1985 and 1995. Mortality from coronary heart disease was, however, about two-fold higher in people with diabetes compared with people without the disease at both time points (Dale et al., 2008). Similar results are seen in a large cohort study from the UK General Practice Research Database (Charlton et al., 2008; Gulliford & Charlton, 2009) where a decline in early mortality for subjects diagnosed with diabetes was observed from 1996 to 2006. After adjusting for age, sex, and diabetes duration, there was a consistent decrease in relative mortality during the period of study. A recent study from the Danish National Diabetic Register persons showed a rise in prevalence of diabetes during 1995-2006 and over the same time mortality rate in diabetic patients decreased faster than that of the non-diabetic population (Carstensen et al., 2008). In a second study from the Danish National Diabetic Register (1995-2008) those with

diabetes had a higher mortality from all the specific causes of death (Hansen et al., 2012) than persons without diabetes.

Changes in mortality risk following a myocardial infarction in persons with and without type 2 diabetes have been used in recent studies to estimate the detrimental effect of diabetes (Koek et al., 2007; Norhammar et al., 2007; Winell et al., 2010). Although these study show a trend towards improved survival in patients with diabetes compared to those without diabetes, an excess mortality risk still remains.

1.8 Role of statin medication in cardiovascular disease and diabetes

In a review article from 2006 J. Shepherd states that the 3-hydroxy-3-methylglutaryl CoA reductase inhibitors or statins are the most successful cardiovascular drugs of all times (Shepherd, 2006). He even claims that the benefits, with little side effect penalty, has resulted in the comparison of statins with antibiotics in the global battle against cardiovascular disease.

Since statins were first used in treating hypercholesterolemia in man in the early 1980s (Mabuchi et al., 1983; Yamamoto et al., 1980) a steadily increasing evidence base has been gathered showing the benefit of statin therapy in reducing cardiovascular disease morbidity and mortality, along with a very low incidence of adverse effects.

Following the multicenter clinical trial of the Scandinavian Simvastatin Study Group performed in the 1990s where the effect of simvastatin on mortality and morbidity was assessed in a group of 4444 patients with coronary heart disease, aged between 35 and 70 years (1994) statins have become the drug of choice in hypercholesterolemia. In a systematic review and meta-analyses of 58 trials of statin therapy (Baigent et al., 2005) there was a proportional reduction in the incidence of coronary and other major vascular events largely irrespective of the initial lipid profile or other presenting characteristics and without any excess risk observed. The authors concluded that statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularisation, and stroke by about one fifth per mmol/L reduction in LDL cholesterol. In a more recent meta-analysis from the Cholesterol Treatment Trialists' Collaboration (Baigent et al., 2010) results from 26 randomised trials on the comparison between more intensive versus standard statin regimens was made. Their major conclusion was that further reduction in LDL cholesterol safely produced definite further reduction in the incidence of heart attack, of revascularisation, and

ischemic stroke, with each 1.0 mmol/L reduction, reducing the annual rate of these major vascular events by just over a fifth.

The benefit of statin therapy in primary prevention in patients without established cardiovascular disease but with cardiovascular risk factors has also been shown in a meta-analysis of randomised controlled trials (Colhoun et al., 2004). In another more recent meta-analysis of 10 trials with a total of 70 388 persons, without established cardiovascular disease but with cardiovascular risk factors, where 23% had diabetes mellitus, statin treatment reduced risk in all-cause mortality, major coronary and cerebrovascular events as well as coronary heart disease mortality, without showing undue adverse effects (Brugts et al., 2009). The risk reduction was similar to what had been reported in trials of patients at relatively low risk in secondary prevention (Cannon et al., 2004). In yet another recent meta-analysis of 18 randomised clinical trials Kostis and co-workers showed that statin therapy was associated with significant decreases in cardiovascular events and in all-cause mortality in women and men in both primary and secondary prevention (Kostis et al., 2012). They concluded that statin therapy should be used in appropriate patients without regard to sex.

In 2005 Lee and co-workers (Lee et al., 2005) addressed the question if everybody with type 2 diabetes should take a statin. They concluded that the benefit of statins might extend beyond a threshold of low-density lipoprotein cholesterol level in patients with type 2 diabetes but more trials would be needed to answer the question. A sustained beneficial effect of statins on mortality and vascular complications as seen in the Steno-2 Study where multi factorial intervention in patients with type 2 diabetes and persistent microalbuminuria (Gaede et al., 2008) showed a reduction both in cardiovascular death (hazard ratio, 0.43) and of cardiovascular events (hazard ratio, 0.41).

In the large scale ACCORD study on an even more intensive lipid lowering medication in patients with type 2 diabetes, where fenofibrate was added to statin medication (Ginsberg et al., 2010), no further reduction in rate of cardiovascular mortality or non-fatal vascular events was observed. Compared with statins alone adding fenofibrate did not support a routine use of this combination therapy in treatment of diabetic patients.

Statin therapy is not without side effects although the proportion of patients with significant statin-associated adverse effects or intolerance is very low. The most common complaint is statin-induced myopathy that can (rarely) manifest with severe and potentially fatal cases of rhabdomyolysis. Mancini and co-workers have published a comprehensive overview of a broad variety of statin-associated adverse effects (Mancini et al., 2011)

including a consensus approach for the prevention, assessment, diagnosis, and management of such effects. The ultimate goal of the review was to ensure that patients who warrant cardiovascular risk reduction can be treated optimally, safely, and confidently with statin medications or alternatives when warranted.

For some years data from clinical trials have been showing conflicting findings on the risk of developing type 2 diabetes when patients are receiving statin medication. Sattar and co-workers have done a meta-analysis of 13 statin trials with 91140 participants to examined if statins increase the risk of incident diabetes (Sattar et al., 2010). They concluded that statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events. However, the data suggest the need to make patients aware of this possible risk and to monitor patients for development of diabetes, especially those on intensive-dose therapy (Preiss et al., 2011).

1.9 Prevention strategies for type 2 diabetes

Much effort has been put into diabetes prevention work both by diverse local efforts (Eriksson et al., 1999) and on the international front, led by the International Diabetes Federation and the World Health Organization. The IDF recommends that all people at high risk of developing type 2 diabetes be identified through opportunistic self-screening using the web-site http://www.idf.org/prevention.

As early as 1991 the Malmö Study in Sweden showed that incidence of type 2 diabetes in men with impaired glucose tolerance could be reduced by 50% after adhering to a diet and exercise programme for 5 years (Eriksson & Lindgarde, 1991). Tuomilehto and co-workers (Tuomilehto et al., 2001) showed in 2001 that type 2 diabetes can be prevented or delayed by weight reduction and changes in the lifestyles in high-risk subjects. The risk of type 2 diabetes was reduced by 58% in an intervention group compared to a control group after a 3.2 year follow up time. Similar results were reported from the United States by the Diabetes Prevention Program Research Group in 2002 (Knowler et al., 2002) where reduction in incidence was observed after life style intervention or by metformin medication. In a meta-analysis of 17 studies in 2006 the authors (Gillies et al., 2007) concluded that lifestyle and pharmacological interventions reduce the rate of progression to type 2 diabetes in people with impaired glucose tolerance. They also found that lifestyle interventions seemed to be at least

as effective as drug treatment. It should be realized, however, that although lifestyle interventions produce successful results in research settings, they are labour intensive and difficult to replicate even in well-funded healthcare systems.

A systematic review of 43 papers on risk models and risk scores for type 2 diabetes was recently published (Noble et al., 2011) where Noble and co-workers conclude that although much work has been done to develop diabetes risk models and scores, most are rarely used. The reason being that either they require tests not routinely available or were developed without a specific user or clear use in mind. A simple Diabetes Risk Score is now available on the internet, developed in the United Kingdom, www.diabetes.org.uk/Risk-Test, and several other easily accessible and successful diabetes risk questionnaire have been developed (Hippisley-Cox et al., 2009; Rahman et al., 2008). The original Finnish diabetes risk questionnaire, a robust tool to predict future screen-detected and clinically diagnosed type 2 diabetes in European population, has now been improved (DETECT-2) and updated by adding information on sex, smoking and family history of diabetes (Alssema et al., 2011). People at high risk of diabetes once identified after self-screening or by a diabetic risk score in the family clinic, should then have their plasma glucose levels measured and prevention efforts set in motion.

For productive actions in the field of preventive medicine as well as health care provision at all levels it is essential to have available accurate local data on the health status of the population at large, along with some indication on how effective the health care provision is in improving the health status and well-being of the people. This information should also be available to the general public thus encouraging them to participate individually in maintaining the best possible well-being for themselves and their dependents.

The National Institute for Health and Welfare in Helsinki has advocated that a comprehensive approach to diabetes prevention should combine population based primary prevention with programmes targeted at those who are at high risk. This approach should take account of the local circumstances and diversity within modern society (e.g. social inequalities). The challenge goes beyond the healthcare system. We need to encourage collaboration across many different sectors: education providers, non-governmental organisations, the food industry, the media, urban planners and politicians. They all have an important role to play as small changes in lifestyle will bring about big changes in improving health. Through joint efforts, more people will be reached; the time to act is now (Lindstrom et al., 2010).

2 AIMS

The first aim of this thesis was to examine if environmental conditions in the first 20 years of life and metabolic conditions in midlife were associated with risk of developing type 2 diabetes later in life. A second aim was to examine the secular trend in mortality rate of older persons with and without diabetes between 1993 and 2004 with respect to changes in cardiovascular risk factor levels and medical treatment.

The specific aims were:

1. To estimate if residency in the first 20 years of life in Iceland (rural, coastal or urban) affected the risk of developing type 2 diabetes.
2. To study at a population based level the metabolic conditions in midlife leading to development of type 2 diabetes later in life.
3. To examine secular trend in mortality rate of older persons with and without type 2 diabetes from 1993 to 2004.
4. To assess the effects of statin medication on mortality risk associated with type 2 diabetes in older persons.

This work is based on data from the population-based Reykjavik and the Age, Gene/Environment Susceptibility-Reykjavik (AGES-Reykjavik) studies.

3 MATERIALS AND METHODS

3.1 Study population

The Reykjavik Study is a population-based cohort study established in 1967 by the Icelandic Heart Association as a long-term prospective cardiovascular survey (Björnsson et al., 1982; Björnsson et al., 1979). All men and women (N=30795) born in 1907-1935 and living in Reykjavik in December 1966 were selected. A random sample of 27281 were invited to attend (3514 kept as a control) and a total of 19381 attended (stages I-VI), resulting in 71% recruitment rate. The cohort was divided into six groups, and examined in six stages. Participants in stages I-V were examined over the period 1967-1991 and in the last stage VI between the years 1991-1996. By that time the participants had reached the mean age of 75 years. Between 2002 and 2006 the AGES-Reykjavik study re-examined 5764 unselected survivors of the original cohort who had previously participated in the Reykjavik Study (Harris et al., 2007).

A schematic description of participants from the Reykjavik Study and the AGES-Reykjavik study analysed in each part of the present thesis (papers I-IV) is given in Table 4.

In paper I data from the five stages (I-V) of the Reykjavik Study conducted between 1967 and 1991 were analysed. Participants provided information on residency from birth across their lifetime. Individuals completed their residence history in an open question listing all places they had lived in for 5 years or more. Although all participants were residing in the greater Reykjavik area in 1967 upon entry to the study, 64% were born and raised elsewhere before moving to the capital. We classified every community as a rural area or a coastal village by using the 1974 National Land Survey of Iceland. To improve the classification further, we used data from the Icelandic Historical Statistics on population density by region in 1940 and fish catch by place of processing in 1942 (StatisticsIceland, 1997). Around 245 communities were classified into 4 categories: Reykjavik, coastal villages, rural areas and combination of coastal villages and rural areas. Rural areas were areas away from the sea or areas by the sea which did not have a fish catch and were classified as rural by the Icelandic Historical Statistics. Coastal villages were coastal areas that had a fish catch and were classified as dense. For the residency analysis, we excluded communities classified as a combination of a rural and sea village, reducing the study cohort to 17811 men and women (mean age 53 years, range 33-81 years). Of those 5195 (29%) grew up in a rural area for a

Table 4. Schematic description of participants from the Reykjavik Study and the AGES-Reykjavik study.

	Paper I	**Paper II**	**Paper III**	**Paper III**	**Paper IV**
	Reykjavik Study stage 1-V 1967-1991	AGES-Reykjavik first part (interim) 2002-2004	Reykjavik Study stage VI 1991-1996	AGES-Reykjavik 2002-2006	AGES-Reykjavik 2002-2006
Attended	18872	2300	1607	5764	5764
Not included	1061 [a)]	49 [b)]	101 [c)]	1444 [d)]	612 [e)]
Included	17811	2251	1506	4320	5152
Age range in years	33-81	65-96	70-87	70-87	66-96
% men	48	43	42	43	43

[a)] as living in a mixed rural and coastal area.

[b)] 21 gave conflicting information on diabetes and 28 had type 2 diabetes when entering the Reykjavik Study.

[c)] 101 outside the age range 70-87 years.

[d)] 950 outside the age range 70-87 years, 494 with one or more missing data on risk factors, missing HbA1c or considered having type 1 diabetes.

[e)] 612 not included, thereof 21 considered having type 1 diabetes, 66 with missing data on diabetes history, 78 with one or more missing data on risk factors, 447 with missing HbA1c.

mean time of 20 years before moving to the city and 6140 (35%) lived in a coastal village for the first 20 years of their life before moving to Reykjavik but 6476 (36%) lived in urban Reykjavik from birth.

In paper II we analysed data from the interim group of men and women participating in the AGES-Reykjavik Study between 2002-2004. From the original study cohort of 2300 individuals, 21 were excluded as they either gave conflicting information about having diabetes, or the questionnaire related to diabetes was not completed. We also excluded 28 subjects who were already diagnosed with type 2 diabetes when first attending the Reykjavik Study. The study cohort therefore consists of 2251 individuals, 956 men and 1395 women, aged 65-96, with an overall response rate of 75% for men and 68% for women. The mean age of this AGES-Reykjavik cohort when first entering the Reykjavik Study was 50 years. At entry in the AGES-Reykjavik study the cohort was divided into three subgroups for both sexes according to their glycemic status, based on the WHO recommendations from 1999 (WHO, 1999). The first group, used as reference, had normal fasting glucose ($\leq$ 6.0mmol/l). The second group had impaired fasting glucose values at the AGES-Reykjavik examination (6.1-6.9mmol/l). The third group, individuals with type 2 diabetes, were either diagnosed upon their visit to the clinic with fasting serum glucose of $\geq$ 7mmol/l, or identified by self-reported diabetes in the questionnaire, use of diabetes medication, or being on a special diet for type 2 diabetes and under regular observation of health professionals.

In paper III we compared data from two non-overlapping cohorts of older people (age range of 70-87 years) examined 11 years apart. The first cohort was from the last stage (VI) of the Reykjavik Study, with 1506 participants, mean age 75.0 years, examined between 1991 and 1996 (median 1993), with a median follow-up period of 5.6 years. The median year of birth was 1919 (inter quartile range 1917-1921). The second cohort was from the AGES-Reykjavik study, with 4320 participants, mean age 76.6 years, examined between 2002 and 2006 (median 2004), and with a median follow up time of 5.3 years. The median year of birth was 1928 (inter quartile range 1924-1931).

Participants in paper IV counted 5152 men and women from the AGES-Reykjavik study, with a mean age of 77 years (range 66-96) and a median follow up time of 5.3 years. In order to exclude any persons with type 1 diabetes in the study, participants reporting onset of diabetes before the age of 40 were not included; neither were participants not completing their questionnaire or having incomplete data for other study variables included: 21 were

considered to have diabetes of type 1; 66 had missing data about diabetes history on questionnaire; 78 had one or more missing data on risk factors (cholesterol, systolic blood pressure, body mass index, triglycerides); 447 had missing HbA1c.

In papers I, III and IV the study cohorts were divided into persons without diabetes and those with type 2 diabetes that were either diagnosed upon their visit to the clinic with fasting serum glucose of ≥ 7mmol/l, based on the WHO recommendations from 1999 (WHO, 1999) or identified by self-reported diabetes in the questionnaire, use of diabetes medication, or being on a special diet for type 2 diabetes and under regular observation of health professionals. Participants reporting onset of diabetes before the age of 40 were not included to exclude possible individuals with type 1 diabetes in the studies.

3.2 Risk factor ascertainment

In all studies blood samples were drawn from participants after overnight fasting.

For the first five stages of the Reykjavik Study chemical analyses were performed on Technicon auto analysers using recommended methodology from the manufactures at each time. In stage VI total cholesterol, HDL cholesterol, triglycerides and glucose were analysed on a COBAS Mira using reagents from Roche Diagnostics. In the AGES-Reykjavik study, total cholesterol, HDL cholesterol, triglycerides, high sensitivity CRP, glucose and HbA1c as well as urinary albumin and creatinine were analysed on a Hitachi 912, using reagents from Roche Diagnostics and following the manufacturer's instructions. LDL was calculated using the Friedewald equation (Warnick et al., 1990). Insulin was measured by an electrochemiluminescence immunoassay on a Roche Elecsys 2010 instrument, using two monoclonal antibodies and a sandwich principle. The method was standardized using the 1st IRP WHO Reference Standard 66/304 (NIBSC). The analytical methods used in the Reykjavik Study have been described elsewhere (Jonsdottir et al., 2002). $HOMA_{IR}$, a measure of the insulin resistance, is calculated using the formula [insulin(mU/l) x glucose(mmol/l)]/22.5 (Matthews et al., 1985). Rigorous internal and external quality control procedures were used to ensure comparable results throughout the long study period.

In paper II metabolic syndrome criteria, as defined by WHO, are used (Alberti et al., 2006). As glucometabolic status at entry had been used to divide the cohort into study groups we decided to omit insulin resistance and glycemic status, and include two or more of the

following criteria: BMI>30kg/m^2; triglycerides≥1.7mmol/l or HDL<0.9, in males, and <1.0mmol/l, in females; hypertension >140/90mmHg; U-albumin/creatinine ≥3.5mg/mmol.

In all studies blood pressure was measured with a mercury sphygmomanometer with a large cuff, and the mean value of two consecutive blood pressure measurements was used in the analysis. A 12 lead resting ECG was evaluated according to the Minnesota code (Jonsdottir et al., 1998). Height and weight were measured and BMI calculated as kg/m^2.

Participants answered questions about frequency of moderate or vigorous physical activity. Answers were categorized into never, rarely, occasionally, moderate or high frequency of participation. A binary variable for physical activity was used as an indicator for occasional or higher frequency of participation versus never or rarely participating.

Answers about education were categorized into a binary variable: higher than secondary education versus secondary education or less.

The coronary events reported are verified myocardial infarcts, coronary artery bypass graft and percutaneous transluminal coronary intervention. Information on the causes of death was based on data from a complete adjudicated registry of deaths available from the Icelandic National Roster (StatisticsIceland). All-cause mortality was defined according to ICD 9-10. In the studies we calculated an individual's time at risk from the date of participation in the baseline survey until the date of death from cardiovascular disease (ICD-9 and ICD-10: defined as in the SCORE project (Conroy et al., 2003)) or from all causes, or until the end of follow-up in the cohort. The information is collected from National Health System Records by the Icelandic Heart Association.

3.3 Statistical analyses

Data were analysed using SAS/STAT® software, version 9.1. or version 9.2. Stata version 12 was also used.

In paper I baseline characteristics of participants by sex and place of residency for the first 20 years of life were compared using either linear or logistic regression with age adjustment. Skewed variables were log-transformed. The Poisson regression model was used to estimate relative risk of developing type 2 diabetes. For relative risk estimates, an adjustment was made for age BMI, triglycerides, systolic blood pressure, and current smoking.

In paper II response variables on a continuous scale were analysed with linear regression models by sex, adjusted for age and a categorical predictor for glycemic status. Binary variables were analysed similarly with logistic regression models. Analyses of change in continuous variables were performed, using mixed effects regression models, adjusted for age and time between visits and a random effect for subjects. All parameters were adjusted to the age of 50 in midlife and a 26-year follow-up. The association of type 2 diabetes in late life with midlife risk parameters was estimated in a multivariable logistic regression model. Skewed variables were log-transformed in all studies.

In paper III baseline characteristics of participants by sex and diabetic status were compared between studies (the last stage (VI) of the Reykjavik Study and AGES-Reykjavik) using either linear or logistic regression with age adjustment. The Cox proportional hazards regression model was used to estimate hazard ratios and mortality rates. Time since entering the study was used as the time scale. For hazard ratio estimates, an adjustment was made for age, sex and history of coronary heart disease (myocardial infarction, percutaneous transluminal coronary intervention or coronary artery bypass graft) in a simple model, and additionally for cardiovascular risk factors: cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, hypertensive medication, and smoking history. For the AGES-Reykjavik data an adjustment was also made for CRP. The mortality rate was estimated from the average of the cumulative hazard function after a 5 year follow-up and represented as the rate per 1000 person years. The proportionality assumption for the hazard ratio associated with type 2 diabetes was inspected graphically. It was also inspected by testing the significance of the interaction of type 2 diabetes status with logarithm of the follow-up of time analysed as a time dependent covariate. All two way interactions between effects of diabetic status and coronary heart disease history on the hazard of death were tested for statistical significance.

In paper IV the Cox proportional hazards regression model was used to estimate mortality rates and hazard ratios for the effect of risk factors and statin use. For hazard ratio estimates, an adjustment was made for age and sex in a simple model, and additionally for the following cardiovascular risk factors: cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, CRP, hypertensive medication, and current smoking. In addition an analysis of mortality rates was done with adjustment for physical activity and education level. A separate term was used in the survival models to represent subgroups, formed by diabetes, history of

CHD and statin use. Significance testing was two-sided in all studies and based on a 5% probability level.

3.4 Ethical considerations

Informed consent was obtained from all study participants. The study was approved by the National Bioethics Committee in Iceland (VSN 00-063) as well as the Institutional Review Board of the Intramural Research Program of the National Institute on Aging and the Data Protection Authority in Iceland.

4 RESULTS

4.1 Early life residency in rural or urban areas associated with long term risk evaluation of type 2 diabetes (Paper I)

The prevalence of type 2 diabetes in men and women from the first five stages of the Reykjavik study, estimated according to area of residency in the first 20 years of life, is shown in Table 5. The mean age of the cohort was 53 years at entry (range 33-81). In men growing up in a rural area the prevalence was 3.0% compared to 4.9% in men living in Reykjavik from birth. In women the prevalence was 2.9% if they grew up in a rural area compared to 3.5% if living in Reykjavik from birth. Correcting for serum triglycerides, BMI and systolic blood pressure the relative risk of developing type 2 diabetes was 45% lower in men (RR 0.55; 95% CI 0.41-0.74) and 27% lower in women (RR 0.72; 95% CI 0.54-0.95) who grew up in rural areas compared to those living in Reykjavik from birth as shown in Table 6.

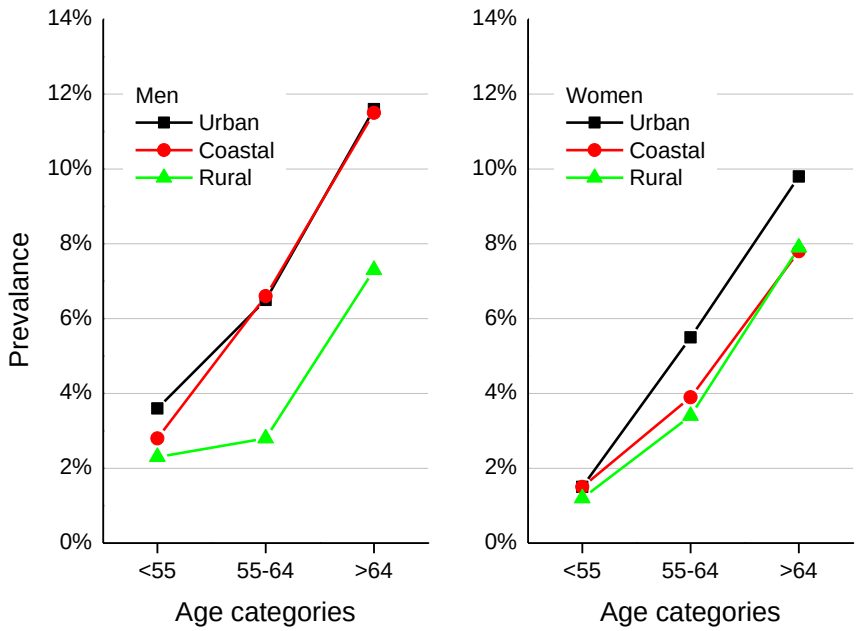


Figure 1. Prevalence of type 2 diabetes in men (a) and women (b) living in urban Reykjavik in 1967, according to age categories and residency for the first 20 years of their life, in a rural area (29%), a coastal area (34%) or in urban Reykjavik (37%) from birth.

Table 5. Prevalence of type 2 diabetes in men and women living in urban Reykjavik in 1967, according to age categories and residency for the first 20 years of their life, in rural areas, coastal villages or in urban Reykjavik. 17 811 men and women born in 1907-1935 examined between 1967 and 1991 with a mean prevalence of 3.6% for type 2 diabetes.

Residency	**Rural**	**Coastal**	**Urban**
Men			
Number	*2415*	*2840*	*2990*
n with T2D	*72*	*132*	*150*
Age in years, mean (± SD)	53.7 (±8.7)	52.2 (±8.5)	51.2 (±8.3)
Age range	34-79	33-78	33-78
% T2D diagnosed at study entry	61.5	66.7	58.5
T2D prevalence % (n)	3.0 (72)	4.6 (132)	5.0 (150)
" at age <55	2.3	2.8	3.6
" at age 55-64	2.8	6.6	6.5
" at age 65+	7.3	11.5	11.6
Women			
Number	*2635*	*3078*	*3227*
n with T2D	*73*	*90*	*109*
Age in years, mean (± SD)	54.2 (±9.1)	53.5 (±8.9)	52.3 (±8.9)
Age range	33-81	33-80	33-80
% T2D diagnosed at study entry	52.1	42.7	40.2
T2D prevalence % (n)	2.8 (73)	2.9 (90)	3.4 (109)
" at age <55	1.2	1.5	1.5
" at age 55-64	3.4	3.9	5.5
" at age 65+	7.9	7.8	9.8

To examine if the difference in prevalence was maintained throughout life the cohort was divided into three cross sectional age groups, <55 years, 55-64 years and >64 years of age and the prevalence estimated as shown in Figure 1 and Table 5. The prevalence of type 2 diabetes in men growing up in a coastal village and in urban Reykjavik is almost the same in the age groups 55 years and older and nearly double that seen in men growing up in a rural area. Women growing up in a coastal village or a rural area have a similar prevalence and considerably lower than those growing up in urban Reykjavik in the age groups 55 years and older.

Table 6. The relative risk (RR) of developing T2D according to residency for the first 20 years of life (rural/urban) with 95% confidence interval.

			95% Confidence Interval		
	Model	**RR**	Lower	Upper	Risk reduction
Men	1	**0.52**	0.39	0.69	48
	2	**0.57**	0.43	0.77	43
	3	**0.56**	0.42	0.76	44
Women	1	**0.70**	0.52	0.93	30
	2	**0.74**	0.56	0.99	26
	3	**0.75**	0.56	1.00	25

Model 1: Adjusted for age.
Model 2: Adjusted for age, BMI, systolic blood pressure and serum triglycerides.
Model 2: Adjusted additionally for smoking status, education and leisure time physical activity.

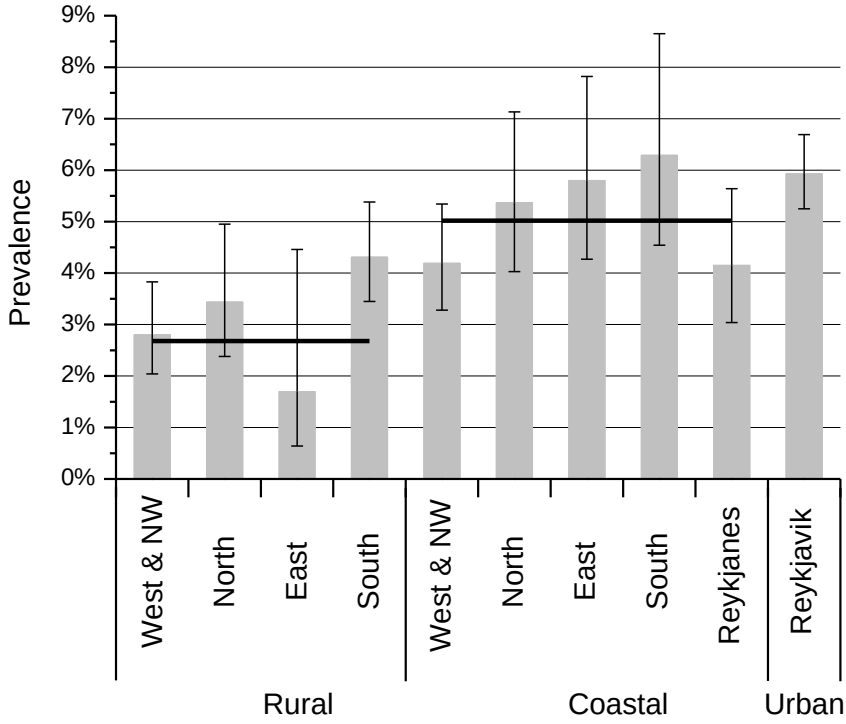


Figure 2. Prevalence of type 2 diabetes, adjusted to sex and the age of 60 years, in men (48%) and women living in urban Reykjavik in 1967 according to residency for the first 20 years of their life in a rural, coastal or urban area. The different regions of the country are subdivided into rural or coastal areas and urban Reykjavik. The two horizontal lines show the adjusted mean prevalence in rural (2.7%) and coastal (5.0%) areas. Each column is shown with error bars (with 95% CI) and numbers of cases behind each column are as follows.
Rural (total 5195): West and Northwest peninsula (1640), North (1002), East (290), South (2263). Coastal (total 6140): West and Northwest peninsula (1918), North (1233), East (935), South (743), Reykjanes peninsula (1311). Urban Reykjavik (6476).

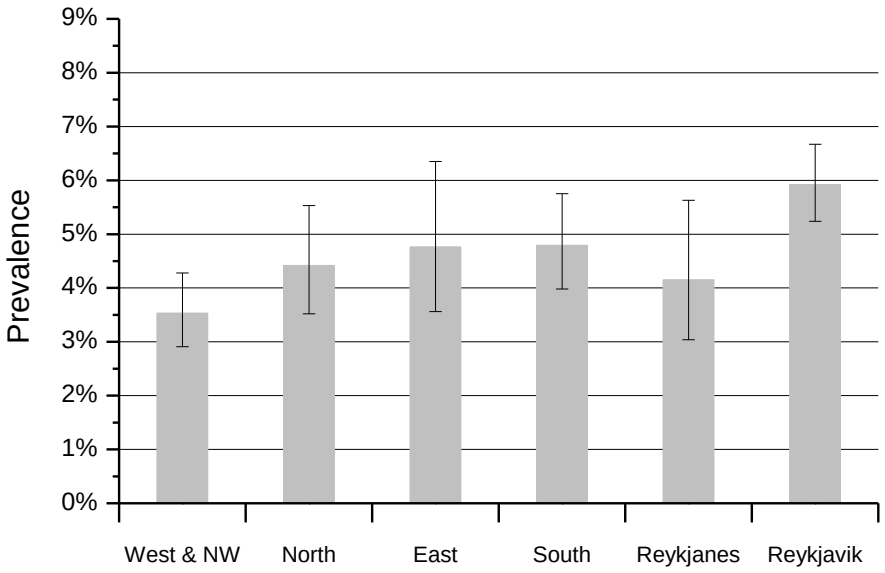


Figure 3. Prevalence of type 2 diabetes, adjusted to sex and the age of 60 years, in men (48%) and women living in urban Reykjavik in 1967 according to residency in different regions of the country for the first 20 years of their life. Each column is shown with error bars (with 95% CI) and numbers of cases behind each column are as follows.
Rural and Coastal areas combined: West and Northwest peninsula (3558), North (2235), East (1225), South (3006), Reykjanes peninsula (1311); Urban Reykjavik (6476).

Baseline characteristics of the individuals when entering the study are shown in Table 7. The mean age of both men and women growing up in a rural area is about 2 years higher than in those living in Reykjavik from birth. Triglyceride levels and BMI are lower in those coming from rural areas but smoking is more common in both men and women living in Reykjavik from birth. Education level in men is similar irrespective of where they grew up with just over 20% with more than secondary education. Women as a whole have a lower education level than men, especially those coming from the coastal areas, where only 6% have more than secondary education compared to 10.8% of those living in urban Reykjavik from birth.

As the living conditions were most certainly different in different parts of the country prevalence was estimated for men and women together coming from rural and coastal areas in different regions as shown in Figure 2 and 3. We saw a striking difference between prevalence of type 2 diabetes in persons who came from rural areas in Eastern Iceland compared to those coming from the southern part of the country. The difference was not as marked between coastal areas, although persons from the Reykjanes peninsula and Western part including the Northwest peninsula have lower prevalence than those coming from the

Table 7. Baseline characteristics when entering the Reykjavik Study (1967-1991) according to residency in a rural coastal or urban area for the first 20 years of life.

	Men			**Women**		
Variables	Rural	Coastal	Urban	Rural	Coastal	Urban
Number	*2847*	*2972*	*3140*	*2708*	*3168*	*3336*
Age in years (±SD)	53.6 (±8.7)	52.3 (±8.6) ***	51.3 (±8.3) ***	54.2 (±9.2)	53.5 (±8.9) *	52.4 (±8.9) ***
Cholesterol, mmol/L (±SD)	6.36 (±1.07)	6.43 (±1.07) *	6.35 (±1.07)	6.65 (±1.22)	6.69 (±1.26) *	6.51 (±1.21) **
Triglycerides, mmol/L, median (IQR)	1.03 (0.65)	1.09 (0.67) ***	1.14 (0.71) ***	0.90 (0.51)	0.92 (0.54) ***	0.93 (0.56) ***
Glucose, mmol/L (±SD)	5.36 (±0.85)	5.40 (±0.87) *	5.46 (±0.94) ***	5.12 (±0.78)	5.18 (±0.83) **	5.18 (±0.89) ***
BMI, kg/m2 (±SD)	25.6 (±3.3)	25.7 (±3.4)	26.0 (±3.6) ***	25.0 (±4.3)	25.2 (±4.3)	25.1 (±4.3) *
Systolic BP, mm Hg (±SD)	140.2 (±19.2)	139.6 (±18.7)	140.9 (±19.5) ***	137.3 (±20.8)	138.2 (±20.9) *	136.6 (±20.2)
Diastolic BP, mm Hg (±SD)	88.1 (±10.3)	87.9 (±10.1)	88.6 (±10.8) *	84.0 (±10.2)	84.3 (±10.3)	84.0 (±10.1)
CHD prevalence[†] %	2.9	3.1	2.6	0.5	0.9*	0.8*
Current smoking %	49.6	56.7***	59.3***	38.5	38.0	44.1***
Education more than secondary %	23.7	20.2***	21.8*	8.1	6.3**	10.8***
Sports activity at 20-29y %	17.0	15.3	21.3***	7.7	7.6	10.7***
Leisure time physical activity at entry %	11.9	10.0*	13.8*	10.0	11.4	14.4***

Significance estimates: *p<.05; **p<.01; *** p<.001 for age-adjusted comparison, rural residency used as reference.

[†] Prevalence from history of MI, PCI, and CABG in hospital records.

North, East and South where the prevalence comes close to what is seen in urban Reykjavik. When coastal and rural areas are combined again persons from the Western part and the Reykjanes peninsula have lower prevalence than those coming from other parts of the country.

4.2 Midlife risk factors related to development of type 2 diabetes in late life (Paper II)

Prevalence of type 2 diabetes

In paper II the study cohort was categorized into subgroups by sex and glycemic status when entering the AGES-Reykjavik study at the mean age of 76 years (range 65-96). Since the mean age of 50, 14.3% of men developed type 2 diabetes, compared with 8.2% in women, thereof 28.4% were diagnosed at study entry. Persons diagnosed with type 2 diabetes at entry did not show any distinct characteristics different from those already diagnosed therefore all type 2 diabetes participants were treated as one group in this study. A positive family history of diabetes was reported by 39.5% of participants with type 2 diabetes, compared with 19.3% in persons with IFG and normol glucose metabolism as seen in Table 8.

Table 8. AGES – Reykjavik participants by glycemic status and family history of diabetes

Glycemic status	**both sexes mean age**	**both sexes % (n)**	**% family history of T2DM**	**men % (n)**	**women % (n)**
Normoglycemic	76 ± 6	75.3 (1695)	19.3	70.6 (675)	78.8 (1020)
IFG	76 ± 6	13.9 (313)	19.3	15.1 (144)	13.1 (169)
Total T2DM	76 ± 5	10.8 (243)	39.5	14.3 (137)	8.2 (106)
(uT2DM)	*77 ± 5*	*3.1 (69)*	*40.6*	*4.0 (38)*	*2.4 (31)*
(dT2DM)	*76 ± 5*	*7.7 (174)*	*39.1*	*10.4 (99)*	*5.8 (75)*
Total number		2251		956	1295

The AGES-Reykjavik study cohort divided into subgroups by glycemic status, as well as by gender.
Total T2DM is also shown divided into diagnosed (*dT2DM*) and undiagnosed (*uT2DM*) groups.
The age in years ± SD is given and also the % reporting family history of T2DM for both genders.

Table 9. Baseline characteristics in midlife at entry in the Reykjavik Study by glycemic status in late life

Variables	**Men**			**Women**		
(mean ± SD, median & quartile range or %)	Normoglycemic	IFG	T2DM	Normoglycemic	IFG	T2DM
(number)	(675)	(144)	(137)	(1020)	(169)	(106)
Age in years	49.3 ± 5.7	48.7 ± 5.6	48.7 ± 5.7	51.5 ± 6.8	51.6 ± 6.7	51.9 ± 5.7
Glucose mmol/l	5.3 ± 0.5	5.6 ± 0.5***	5.7 ± 0.6***	5.1 ± 0.5	5.4 ± 0.6***	5.4 ± 0.6***
IFG % (n)	0.6 (4)	2.1 (3)	8.0 (11)	0.4 (4)	1.8 (3)	2.8 (3)
Systolic BP mmHg	133.1 ± 16.9	139.3 ± 17.3***	142.8 ± 19.2***	125.8 ± 17.7	131.9 ± 21.7***	135.2 ± 24.0***
Diastolic BP mmHg	86.1 ± 9.9	89.4 ± 10.9***	91.8 ± 11.8***	80.0 ± 10.3	82.5 ± 10.5**	84.5 ± 11.4***
% on HT medication	1.9	5.6	5.8	5.6	9.5	10.4
BMI kg/m^2	25.0 ± 2.9	26.0 ± 3.0***	26.9 ± 3.0***	24.3 ± 3.6	25.9 ± 3.6***	26.7 ± 3.8***
Hypertension %	48.3	56.2	56.9	47.2	50.3	57.6
Triglycerides mmol/l[b)]	1.0 (0.6)	1.1 (0.7)**	1.3 (0.8)***	0.8 (0.4)	1.0 (0.6)***	1.1 (0.6)***
Cholesterol mmol/l	6.4 ± 1.0	6.5 ± 1.1	6.4 ± 0.9	6.3 ± 1.2	6.4 ± 1.2	6.3 ± 1.1
Smoking % current	51.1	50.7	56.9	29.8	31.4	32.1
Smoking % never	25.8	22.9	22.6	53.1	47.3	53.8

Glycemic groups according to current glycemic status, based on WHO recommendations from 1999.

All values are from the midlife entry in the Reykjavik Study and are mean ± SD unless otherwise indicated.

[b)]Median and (quartile range).

Significance estimates: *p<.05; **p<.01; *** p<.001 for age-adjusted comparison among the study groups.

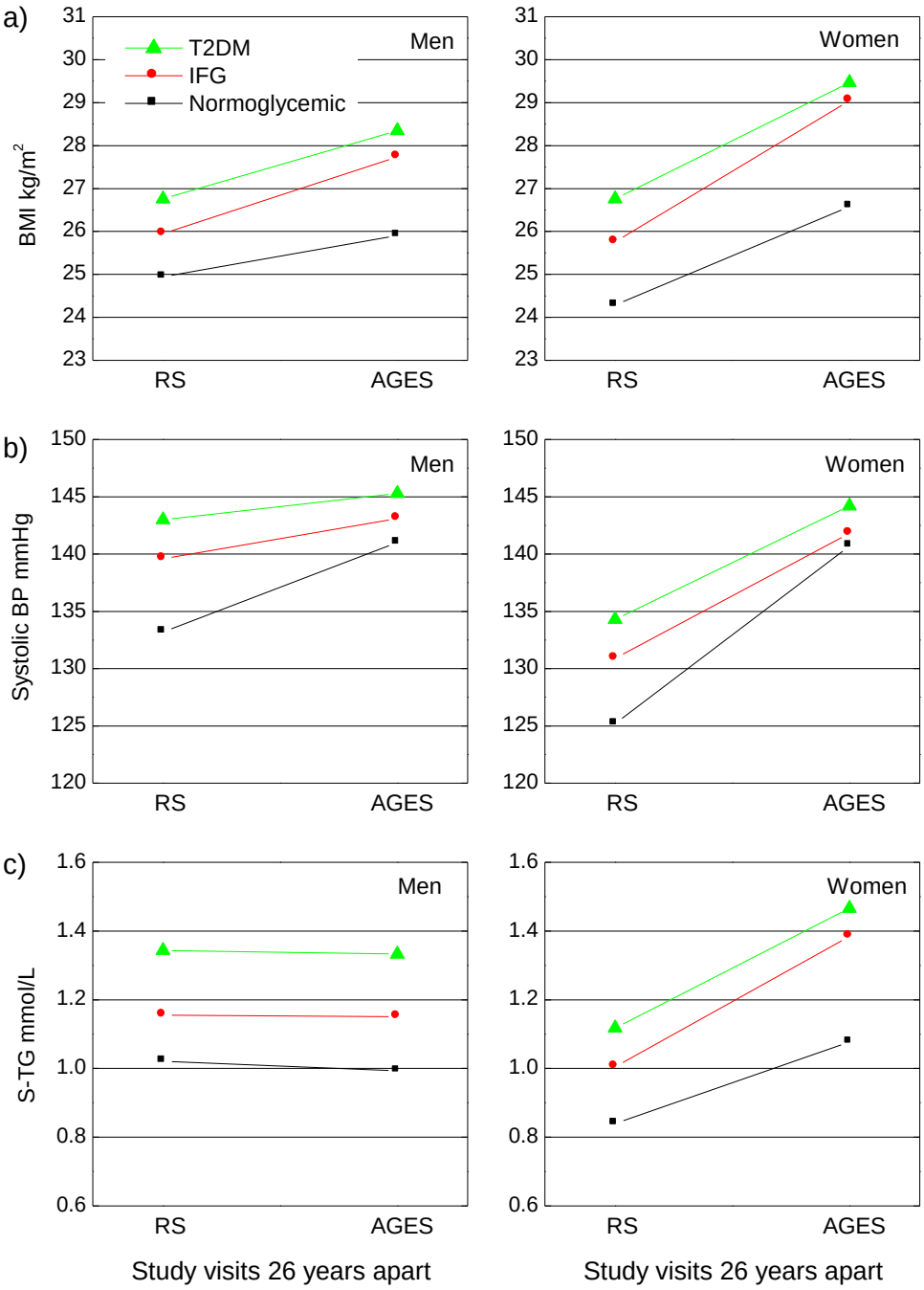


Figure 4. Change in age-adjusted mean of BMI (a) mean Systolic Blood Pressure (b) and geometric mean of S-Triglycerides (c) from the time of first visit in RS to the AGES visit, from the mean age of 50 to 76 years. Grouped by glycemic status and gender.
The increase in mean BMI is significant (p<.0001) in all subgroups of men and women over the period of 26 years. Increase in mean Systolic Blood Pressure is also significant (p<.0001) in all subgroups of men and women. The change in the geometric mean of TG in men over the period of 26 years is not significant. In women the increase of geometric mean levels in TG is highly significant in all subgroups (p<.0001) over the period of 26 years.

Change in risk parameters from midlife to late life

In midlife the mean BMI in both men and women who developed type 2 diabetes was significantly higher than in persons with normal glucose metabolism (Table 9). The same was observed for systolic blood pressure and serum triglycerides. A significant increase in BMI had occurred in all subgroups ($p<.0001$) in late life, with a greater weight gain in persons with IFG and type 2 diabetes than in those that remained normoglycemic ($p<.0001$ for men and $<.0005$ for women) as shown in Figure 4a and Table 10.

Mean systolic blood pressure developed in a similar fashion in both men and women who developed IFG and type 2 diabetes as illustrated in Figure 4b. Both men and women that remained normoglycemic had a significantly lower systolic blood pressure in midlife but the difference diminished in late life. Both men and women developing IFG and type 2 diabetes in late life had significantly higher TG levels in midlife than the respective normoglycemic persons ($p<.0001$) as shown in Figure 4c. In all subgroups of women there was a highly significant increase in TG levels ($p<.0001$) over the 26 years, but not so in men. Cholesterol levels in late life had decreased significantly ($p<.0001$) in all subgroups compared to midlife values and most prominently in those with type 2 diabetes (Table 10).

Odds ratios for the association of type 2 diabetes in late life with midlife risk parameters are summarized in Table 11; they were estimated using a multivariable logistic regression model with adjustment for sex and age at entry in the Reykjavik Study. Variables are listed by the strength of the association.

Glucometabolic status and cardiovascular measures in late life

In addition to fasting serum glucose the glucometabolic status was assessed by mean values of fasting serum insulin along with calculated $HOMA_{IR}$ and blood HbA_{1c} (Table 11). A highly significant difference is found in fasting insulin levels and $HOMA_{IR}$ between the normoglycemic and the groups with impaired glucose regulation, but the level in persons with diabetes is not significantly different from the IFG groups. A stepwise increase was observed in HbA_{1c} values, increasing from the normoglycemic to the IFG and the diabetic men and women. The WHO metabolic syndrome criteria were also estimated (with glucose level and insulin resistance omitted) showing about 60% of the type 2 diabetes groups and almost 50% of the IFG groups with 2 or more MS criteria, compared to 25% of persons in the normoglycemic subgroups (Table 11).

Table 10. Cardiovascular measures by glycemic status in men and women at entry in AGES-Reykjavik

Variables	**Men**			**Women**		
(mean ± SD, median & quartile range or %)	Normoglycemic	IFG	T2DM	Normoglycemic	IFG	T2DM
(number)	(675)	(144)	(137)	(1020)	(169)	(106)
Glucose mmol/l	5.4 ± 0.4	6.4 ± 0.2 ***	7.9 ± 1.8 ***	5.3 ± 0.4	6.4 ± 0.2 ***	7.5 ± 1.8 ***
Insulin mU/l [a)]	8.6 ± 5.8	12.9 ± 6.1 ***	15.7 ± 10.3 ***	8.3 ± 5.4	14.6 ± 9.2 ***	14.9 ± 9.2 ***
HOMA-IR	2.2 ± 1.8	4.3 ± 4.6 ***	6.7 ± 7.4 ***	2.0 ± 1.5	4.2 ± 2.9 ***	5.3 ± 4.1 ***
HbA_{1c} %	5.6 ± 0.3	5.8 ± 0.3 ***	6.6 ± 0.8 ***	5.7 ± 0.3	5.9 ± 0.4 ***	6.3 ± 0.7 ***
% on diabetic medication (only the dT2DM)	-	-	82.8	-	-	52.0
Systolic BP mmHg	141.2 ± 20.7	143.0 ± 20.3	145.1 ± 20.0	140.9 ± 20.9	141.7 ± 22.7	144.2 ± 20.8 *
Diastolic BP mmHg	75.8 ± 9.3	77.4 ± 9.4	74.6 ± 9.4	72.1 ± 9.3	72.4 ± 8.7	72.3 ± 10.1
% on HT medication	56.2	66.7 *	78.1 ***	61.3	68.1	84.9 ***
BMI kg/m^2	26.0 ± 3.5	27.9 ± 3.6 ***	28.5 ± 4.0 ***	26.5 ± 4.7	29.0 ± 4.9 ***	29.5 ± 5.4 ***
Hypertension %	75	85	91 **	77	83**	91 **
Triglycerides mmol/l [b)]	0.97 (0.58)	1.13 (0.61) ***	1.34 (0.91) ***	1.04 (0.64)	1.35 (0.81) ***	1.47 (0.98) ***
Cholesterol mmol/l	5.3 ± 1.0	5.3 ± 1.1	5.0 ± 1.1 ***	6.1 ± 1.1	6.2 ± 1.1	5.7 ± 1.1 ***
HDL-Chol mmol/l	1.43 ± 0.39	1.36 ± 0.39 *	1.25 ± 0.32 ***	1.75 ± 0.43	1.59 ± 0.40 ***	1.50 ± 0.43 ***
LDL-Chol mmol/l	3.40 ± 0.94	3.34 ± 0.97	3.06 ± 0.99 ***	3.86 ± 0.99	3.93 ± 1.05	3.41 ± 0.99 ***
% on statin medication	23.6	29.2	37.2 **	14.8	10.7	24.5 **
% with ≥ 2 MS criteria [c)]	24.4	47.9 ***	58.4 ***	28.1	49.1 ***	63.2 ***
U-Albumin/creatinine mg/mmol % ≥3.5	9.6	13.2	26.1 ***	5.3	8.0	12.5 **
Smoking % current	14.2	9.1	13.1	12.2	13.8	12.3
Smoking % never	23.0	14.8 *	19.0	53.7	44.9 *	50.0

Glycemic groups, based on WHO recommendations from 1999. All values shown are mean ± SD unless otherwise indicated.

[a)]For insulin the truncated mean is used, excluding values >60 mU/L. [b)]Median and (quartile range). [c)]With two or more of the metabolic syndrome criteria, other than insulin resistance and glycemic status, as listed in materials and methods; i.e. BMI, TG, HDL, HT, U-albumin/creatinine.

Significance estimates: *p<.05; **p<.01; *** p<.001 for age-adjusted comparison among the study groups.

Table 11. Odds ratios for the association of T2DM in late life with midlife risk parameters

Risk parameter	Odds Ratio	Lower	Upper	p-value
Glucose (1 mmol/l)	2.94	2.15	4.04	<0.0001
TG (0.1 mmol/l)	1.10	1.06	1.13	<0.0001
BMI (1 unit, kg/m^2)	1.10	1.05	1.14	<0.0001
Systolic BP (10 mmHg)	1.15	1.06	1.24	0.0002
Family history	1.85	1.17	2.91	0.0083
Smoking	1.30	0.96	1.76	0.0846

Odds ratios are estimated using a multivariable logistic regression model with adjustment for sex and age at entry into the Reykjavik Study.
Variables are listed by the strength of the association (p-value).

Table 12. CRP and indicators of cardiovascular disease by glycemic status, at entry in AGES-Reykjavik

Variables	Normoglycemic	IFG	dT2DM
men (n)	(675)	(144)	(137)
CRP mg/L[a)]	1.90 (2.40)	2.10 (3.00)	1.90 (2.60)
CVD[b)] questionnaire %	35.4	35.4	38.0
Heart failure questionnaire %	3.5	5.6	11.9 ***
Abnormal ECG %	58.5	64.3	70.9 **
women (n)	(1020)	(169)	(106)
CRP mg/L[a)]	1.80 (2.80)	2.40 (3.10) *	2.75 (4.30) ***
CVD[b)] questionnaire %	16.8	13.0	25.5 *
Heart failure questionnaire %	2.7	5.4	3.9
Abnormal ECG %	44.1	42.8	48.1

[a)] Median and (quartile range).

[b)] CVD : self-reported stroke, transient ischemic attack (TIA) and cardiac event.

Glycemic groups based on WHO recommendations from 1999.

Significance estimates: *p<.05; **p<.01; *** p<.001 for age-adjusted comparison among the study groups using age-adjusted logistic regression and Chi^2 analysis for MI and AF in women.

Over 35% of men reported a CVD event (cardiovascular disease and stroke) with no significant difference between subgroups (Table 12). A significantly higher proportion of men with type 2 diabetes reported heart failure ($p<.001$) than normoglycemic men and similarly a significantly higher proportion had an abnormal ECG ($p<.01$). No significant difference was seen in current CRP levels in the three subgroups of men. In contrast a significant stepwise increase in CRP levels was seen in women when going from normoglycemic to IFG and type 2 diabetes groups. Women reported lower prevalence of CVD than men in all subgroups, but women with type 2 diabetes have a significantly higher prevalence ($p<0.05$) of both self-reported CVD compared with IFG and normoglycemic women. No significant difference, however, was seen in abnormal ECG in the three subgroups of women.

4.3 Secular trend in mortality risk associated with type 2 diabetes in older persons between 1993 and 2004 (Paper III)

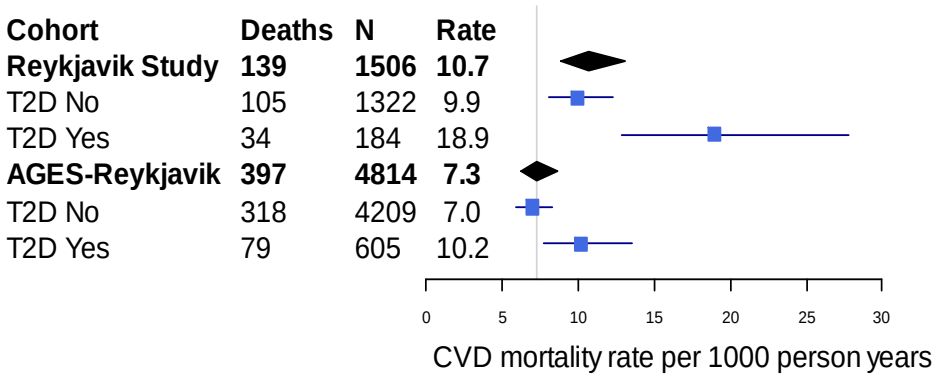
Changes in cardiovascular and all-cause mortality rates between 1993 and 2004

Between the last stage (VI) of the Reykjavik Study in 1993 and the AGES-Reykjavik study in 2004 a secular decline was observed in mortality rates in older persons (age range of 70-87). The decline was 32% (95% CI 14% - 45%) in cardiovascular mortality and 19% (95% CI 6% - 30%) in all-cause mortality rates, as illustrated in Figure 5. Rates were adjusted to age 75, sex (male 43%), the mean levels of cardiovascular risk factors (cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, and smoking history), as well as hypertensive and statin medication within each cohort. A comparable decline is seen in the Icelandic population between 1993 and 2004 according to Statistics Iceland (StatisticsIceland) where the CVD mortality rates for age 70-87 fell by 36% (95% CI 25% - 45%) and all-cause mortality by 21% (95% CI 14% - 28%).

To evaluate the contribution of changes in risk factor levels over time, the mortality rates were compared after adjusting for the common mean values of the risk factors over cohorts. A moderate attenuation was seen and the decline estimated to be 25% (95% CI 3% - 42%, bootstrap 2% - 43%) for cardiovascular mortality and 16% (95% CI 1% - 29%, bootstrap 2% - 28%) for all-cause mortality.

To examine if the decline in mortality affected equally those with and without type 2 diabetes, the cohorts were stratified accordingly. Both cardiovascular and all-cause mortality

a)



b)

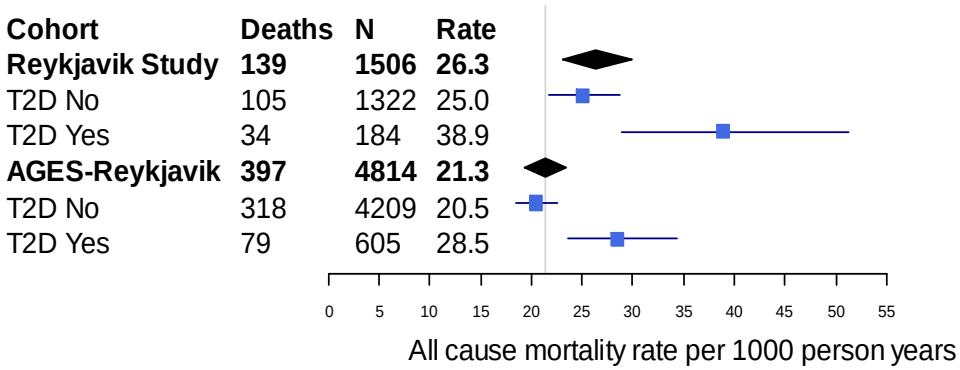


Figure 5. a) Cardiovascular disease (CVD) mortality rate and b) all cause mortality rate per 1000 person years. Rates have been adjusted to age 75, sex and the mean levels of cardiovascular risk factors (cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, and smoking history), hypertensive and statin medication within each cohort. Follow up was a median period of 5.7 years for the Reykjavik Study and a median period of 5.3 years for the AGES-Reykjavik study. The vertical lines represent the mortality rate of the AGES-Reykjavik cohort (N=4814). T2D No, subcohorts without diabetes, T2D Yes, subcohorts with diabetes.

Table 13. Hazard ratios (HR) with 95% confidence interval (CI) for the relative risk of cardiovascular disease (CVD) mortality and all-cause mortality in people with type 2 diabetes (T2D) in the Reykjavik Study from 1991-1996 and the AGES-Reykjavik study from 2002-2006 compared to those without diabetes in each cohort.

	Adjusted for age, sex		Adjusted for age, sex, and CVD risk factors*		Adjusted for age, sex, CVD risk factors*, surgical treatments† and HTNmed‡		Adjusted for age, sex CVD risk factors*, surgical treatments†, HTN med‡ and statin use	
	HR	95% CI	**HR**	95% CI	**HR**	95% CI	**HR**	95% CI
Death from CVD								
Reykjavik Study T2D vs. non-diabetics	**2.21**	1.46-3.34	**1.88**	1.24-2.85	**1.89**	1.25-2.87	**1.89**	1.24-2.86
AGES T2D vs. non-diabetics	**1.69**	1.30-2.20	**1.46**	1.11-1.91	**1.46**	1.12-1.92	**1.47**	1.12-1.93
Death from all causes								
Reykjavik Study T2D vs. non-diabetics	**1.66**	1.23-2.25	**1.55**	1.14-2.11	**1.56**	1.15-2.11	**1.54**	1.13-2.09
AGES T2D vs. non-diabetics	**1.47**	1.23-1.75	**1.38**	1.15-1.65	**1.38**	1.15-1.65	**1.39**	1.16-1.67

*CVD risk factors: cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, and smoking history.

†Percutaneous coronary intervention, and coronary-artery bypass grafting. ‡HTN med: hypertensive medication

rates declined in either group between the two studies (Figure 5), but the decline was greater in individuals with type 2 diabetes, albeit not statistically significant. From 1993 to 2004 a decline of 46% (95% CI 17% - 65%) was observed in cardiovascular mortality rate in persons with diabetes and for individuals without diabetes the decrease in cardiovascular mortality rate was 29% (95% CI 10% - 45%). A comparable reduction was seen for all-cause mortality rate with a 27% (95% CI -10% - 46%) decline in persons with type 2 diabetes compared to 18% (95% CI 4% to 30%) for persons without type 2 diabetes.

Further comparison between the two time periods was done by examining hazard ratios for the relative risk of cardiovascular and all-cause mortality with respect to diabetes (Table 13). The hazard ratios for the relative risk of death from cardiovascular disease, adjusted for age and sex fell from 2.21 (95% CI 1.46 - 3.34) in the Reykjavik Study (1993) to 1.69 (95% CI 1.30 - 2.20) in the AGES-Reykjavik study (2004). When additionally adjusted for cardiovascular risk factors the hazard ratios fell from 1.88 (95% CI 1.24 - 2.85) in the Reykjavik Study to 1.46 (95% CI 1.11 - 1.91) in the AGES-Reykjavik study. No further attenuation was seen after additional adjustment for surgical treatment (percutaneous coronary intervention and coronary-artery bypass grafting), hypertensive and statin medication.

The hazard ratios for relative risk of death from all causes declined in a similar fashion or from 1.66 (95% CI 1.23 - 2.25) in 1993 to 1.47 (95% CI 1.23 - 1.75) in 2004 when adjusted for age and sex. After additional adjustment for cardiovascular risk factors the hazard ratio descended from 1.55 (95% CI 1.14 - 2.11) to 1.38 (95% CI 1.15 - 1.65). This 11% (bootstrap 95% CI -26% - 37%, naïve 95% CI -24% - 37%) decline in mortality ratio did not reach statistical significance.

Changes in cardiovascular risk factors and medication between 1993 and 2004

A decrease in the major cardiovascular risk factor levels (cholesterol, triglycerides, systolic blood pressure and smoking) was observed in men and women between the study periods as shown in Table 14. When the cohorts were stratified according to persons with and without diabetes, individuals with type 2 diabetes had consistently higher baseline levels of triglycerides, BMI and systolic blood pressure at both time points compared to those without diabetes. Cholesterol levels, however, were lower in persons with type 2 diabetes as seen in Table 15.

In 1993 the prevalence of coronary heart disease, obtained from hospital records, was similar in those with and without diabetes in either sex, or about 17% in men and 5% in

Table 14. Baseline characteristics of men and women in the Reykjavik Study (RS) from 1991-1996 (median 1993) and the AGES-Reykjavik study from 2002-2006 (median 2004).

	Men		**Women**	
Variables (mean ± SD, IQR or %)	RS	AGES	RS	AGES
(number)	(636)	(2068)	(870)	(2746)
Age in years	74.6 (±3.4)	77.0 (±4.5) ***	75.3 (±3.7)	77.3 (±4.7) ***
Cholesterol mmol/l	5.99 (±1.06)	5.18 (±1.08) ***	7.03 (±1.24)	5.95 (±1.13) ***
HDL cholesterol mmol/l	1.13 (±0.32)	1.41 (± 0.39) ***	1.50 (±0.42)	1.72 (±0.44) ***
TG mmol/l, median (IQR)	1.13 (0.63)	1.01 (0.64) ***	1.24 (0.70)	1.09 (0.67) ***
CRP mg/l, median (IQR)	-	1.80 (2.50)	-	2.00 (3.00)
BMI kg/m^2	26.1 (±3.7)	26.8 (±3.8) ***	26.4 (±4.8)	27.2 (±4.8) ***
Systolic BP mm Hg	152 (±23)	143 (± 20) ***	148 (±21)	142 (±21) ***
Diastolic BP mm Hg	86 (±11)	76 (± 10) ***	80 (±10)	72 (± 10) ***
Hypertension (%)[†]	80.3	79.9	76.0	82.4
Hypertensive medication (%)	28.3	62.8 ***	36.1	66.4***
Lipid lowering medication (%)	2.1	28.2***	1.8	18.9***
Prevalence of CHD (%)[‡]	17.3	25.7	4.6	8.7
Prevalence of MI (%)[‡]	13.4	12.8	3.9	4.9
Family history MI (%)	25.3	34.6***	29.5	43.0***
Smoking current (%)	20.0	10.4 ***	17.0	11.7**
Haemoglobin A1c (%)	-	5.69 (±0.56)	-	5.69 (±0.32)
Glucose mmol/l	6.17 (±1.29)	5.95 (±1.30) **	5.71 (±1.07)	5.66 (±1.07)

Significance estimates: *p<.05; **p<.01; *** p<.001 for age-adjusted comparison between the Reykjavik Study and AGES.

[†] Hypertension, those with systolic BP>140 mmHg, diastolic BP>90 mmHG or on hypertensive medication.

[‡]Prevalence from hospital records of those with history of myocardial infarction (MI), percutaneous coronary intervention, and coronary-artery bypass grafting.

women. In 2004, however, the prevalence of coronary heart disease in those with diabetes had risen to 32% in men and 14% in women compared to 25% in men and 8% and women without diabetes. At the same time little change was seen in the prevalence of myocardial infarction, except in women with diabetes, where almost twice as many had experienced a myocardial infarction in 2004 (Table 15) compared to 1993.

Prevalence of type 2 diabetes was about the same in both cohorts as shown in Table 16. The proportion of persons with type 2 diabetes already diagnosed at baseline increased from 41% in 1993 to 70% in 2004, as did the proportion of persons already diagnosed and receiving glucose lowering medication. In 1993 only 59% of men with prior diagnosis of type 2 diabetes were on glucose lowering medication compared to 76% in 2004. Similarly 31% of women with diagnosed type 2 diabetes in 1993 were on glucose lowering medication compared to 70% in 2004 (Table 16).

Table 15. Baseline characteristics of men and women with (T2Dyes) and without type 2 diabetes (T2Dno) in the Reykjavik Study from 1991-1996 (median 1993) and the AGES-Reykjavik study (AGES) from 2002-2006 (median 2004).

	Men				**Women**			
	Reykjavik Study		AGES		Reykjavik Study		AGES	
Variables (mean ± SD, IQR or %)	T2Dno	T2Dyes	T2Dno	T2Dyes	T2Dno	T2Dyes	T2Dno	T2Dyes
(number)	(530)	(106)	(1738)	(330)	(792)	(78)	(2471)	(275)
Age in years	74.7 (±3.5)	74.1 (±3.3) *	77.0 (±4.5)	77.1 (±4.4)	75.3 (±3.6)	75.7 (±4.1)	77.3 (±4.7)	77.9 (±4.5)*
Cholesterol mmol/l	6.01 (±1.05)	5.91 (±1.12)	5.23 (±1.07)	4.92 (±1.12) ***	7.03 (±1.25)	6.97 (±1.18)	6.00 (±1.10)	5.53 (±1.13) ***
HDL cholesterol mmol/l	1.14 (±0.31)	1.05 (± 0.35) *	1.42 (±0.40)	1.25 (±0.32) ***	1.52 (±0.41)	1.34 (±0.47) ***	1.74 (±0.44)	1.52 (±0.43) **
TG mmol/l, median (IQR)	1.07 (0.61)	1.43 (1.05) ***	0.98 (0.57)	1.30 (0.88) ***	1.21 (0.66)	1.80 (1.30) ***	1.05 (0.64)	1.40 (0.84) ***
CRP mg/l, median (IQR)	-	-	1.80 (2.60)	1.90 (2.70)	-	-	1.90 (2.90)	2.80 (4.60)
BMI kg/m^2	25.9 (±3.6)	27.5 (±3.9) ***	26.5 (±3.7)	28.4 (±4.1) ***	26.2 (±4.5)	29.1 (±6.1) ***	26.9 (±4.7)	29.5 (±5.2) ***
Systolic BP mm Hg	150 (±22)	159 (± 26) **	142 (±20)	145 (±21) *	148 (±21)	152 (±19)	142 (±21)	144 (±21)
Diastolic BP mm Hg	85 (±10)	88 (± 11) **	76 (±11)	75 (±11) **	80 (±10)	81 (± 11)	72 (± 9)	70 (±10) **
Hypertension (%)[†]	79.2	85.8	77.8	91.1	75.0	85.9	81.3	91.9 ***
Hypertensive medication (%)	26.8	35.8	59.2	79.7***	34.8	48.7*	63.8	83.8 ***
Lipid lowering medication (%)	1.9	2.8	27.3	37.7	2.0	0	17.7	37.0***
Prevalence of CHD (%)[‡]	17.4	17.0	24.8	31.8**	4.6	5.1	8.3	14.0*
Prevalence of MI (%)[‡]	13.4	13.2	12.4	14.6	3.9	3.9	4.6	7.6
Family history MI (%)	26.0	21.7	34.1	37.7**	29.3	32.1	42.6	49.8 **
Smoking current (%)	17.6	20.8	11.0	9.2	17.6	11.5	12.5	9.8
Haemoglobin A1c (%)	-	-	5.55 (±0.31)	6.44 (±0.83) ***	-	-	5.61 (±0.32)	6.42 (±0.88) ***
Glucose mmol/l	5.77 (±0.48)	8.16 (±2.01) ***	5.58 (±0.51)	7.91 (±2.16) ***	5.51 (±0.56)	7.79 (±2.24) ***	5.43 (±0.51)	7.73 (±2.09) ***

Significance estimates: *p<.05; **p<.01; *** p<.001 for age-adjusted comparison between the Reykjavik Study and AGES.

[†] Hypertension, those with systolic BP>140 mmHg, diastolic BP>90 mmHG or on hypertensive medication.

[‡]Prevalence from hospital records of those with history of myocardial infarction (MI), percutaneous coronary intervention, and coronaryartery bypass grafting.

Table 16. Prevalence of type 2 diabetes (T2D) and glucose lowering treatment in the two cohorts, the Reykjavik Study and the AGES-Reykjavik study. The mean duration of T2D is given for those with prior diagnosis at study entry.

Reykjavik Study 1991-1996 (median 1993)	**Men**	**Women**	**Men and women**	**% of total T2D**
	N=636	N=870	N=1506	
Total T2D, prevalence % (*n*)	16.7 (*106*)	9.0 (*78*)	12.2 (*184*)	100
Diagnosed at study entry % (*n*)	10.5 (*67*)	4.8 (*42*)	7.2 (*109*)	59
With prior T2D diagnosis % (*n*)	6.1 (*39*)	4.1 (*36*)	5.0 (*75*)	41
mean T2D duration in years (±SD)			10.1 (±9.4)	
Glucose lowering treatment in prevalent T2D				
% on glucose lowering medication (*n*)	59 (*23*)	31 (*11*)		
% on special diet only (*n*)	41 (*16*)	69 (*25*)		
AGES 2002-2006 (median 2004)	**Men**	**Women**	**Men and women**	**% of total T2D**
	N=2068	N=2746	N=4814	
Total T2D, prevalence % (*n*)	16.0 (*330*)	10.0 (*275*)	12.6 (*605*)	100
Diagnosed at study entry % (*n*)	4.7 (*97*)	3.0 (*83*)	3.7 (*180*)	31
With prior T2D diagnosis % (*n*)	11.3 (*233*)	7.0 (*192*)	8.8 (*425*)	69
mean T2D duration in years (±SD)			10.7 (±10.0)	
Glucose lowering treatment in prevalent T2D				
% on glucose lowering medication (*n*)	76 (*161*)	70 (*112*)		
% on special diet only (*n*)	24 (*52*)	30 (*48*)		

An increase in hypertensive medication observed between 1993 and 2004 was more marked in individuals with diabetes than without, although increase is seen in all groups (Table 15). Over the same time period a decrease in mean values of systolic blood pressure was observed. As for statin medication, about 44% of individuals with known diabetes in 2004 were on statins, but statins were not reported in the 1993 study, while other lipid lowering medication was used by 3% of individuals with known diabetes and under 2% of all participants. Only 27% of men and 18% of women without diabetes were statin users. Individuals using statin medication had 1.26 (95% CI 1.19 - 1.32) mmol/L lower mean cholesterol levels, irrespective of their diabetic status.

4.4 Effects of statin medication on mortality risk associated with type 2 diabetes in older persons (Paper IV)

Risk factors and use of statin medication in type 2 diabetes

The baseline characteristics in men and women from 5152 participants in the AGES-Reykjavik study with a mean age of 77.0 (±5.8) years with and without type 2 diabetes according to statin use are shown in Table 17. A higher percentage of individuals with type 2 diabetes were hypertensive than those without diabetes; they also had lower HDL-cholesterol but higher triglycerides and BMI, irrespective of statin use. Statin medication reduced the mean level of total and LDL-cholesterol by about 1.2 mmol/l in both men and women. In statin users CRP was lower by 0.30 mg/l in men and 0.50 mg/l in women without diabetes and 0.80 and 1.05 mg/l respectively in those with diabetes. The prevalence of coronary heart disease estimated from hospital records in persons without diabetes using statins, was 71.1% in men and 34.4% in women compared to 7.9% and 2.2% respectively in those not using statins. In individuals with diabetes the coronary heart disease prevalence was 59.4% in men and 24.2% in women using statins, compared to 14.8% and 8.6% respectively in those not on statins. Over 93% of all statin users were hypertensive compared to 78% of non-statin users.

The prevalence of type 2 diabetes and use of glucose lowering treatment in men and women is shown in Table 18. About 16% of men and 9.5% of women in the cohort had type 2 diabetes and the proportion of persons with diabetes undiagnosed at baseline was 31%. In the group with previously diagnosed type 2 diabetes, 23% of the men and 35% of the women controlled their blood sugar level with diet only. As shown in Table 18, less than 7% of

Table 17. Baseline characteristics according to statin use in men and women without and with type 2 diabetes (T2D). The AGES-Reykjavik study from 2002-2006.

Variables	**Men**				**Women**			
	Statins no		Statins yes		Statins no		Statins yes	
(mean ± SD, IQR or %)	Without T2D	With T2D	Without T2D	With T2D	Without T2D	With T2D	Without T2D	With T2D
(number)	(1357)	(230)	(477)	(128)	(2237)	(186)	(442)	(95)
Age in years	77.4 (±5.8)	77.9 (±6.1)	76.0 (±4.8)	75.5 (±4.4)	77.0 (±6.1)	78.7 (±6.0) ***	76.1 (±4.8)	76.3 (±4.5)
Cholesterol mmol/l	5.57 (±0.93)	5.38 (±0.98) **	4.32 (±0.82)	4.14 (±0.84) *	6.19 (±1.05)	5.97 (±1.01) **	4.96 (±0.83)	4.67 (±0.94) **
HDL cholesterol mmol/l	1.46 (±0.40)	1.26 (±0.34) ***	1.40 (±0.37)	1.26 (±0.33) ***	1.75 (±0.45)	1.53 (±0.41) ***	1.70 (±0.40)	1.48 (±0.41) ***
LDL cholesterol mmol/l	3.61 (±0.85)	3.40 (±0.89) **	2.38 (±0.67)	2.21 (±0.68) **	3.90 (±0.98)	3.73 (±0.91) *	2.71 (±0.72)	2.41 (±0.70) ***
TG mmol/l, median (IQR)	0.97 (0.56)	1.33 (0.83) ***	1.01 (0.65)	1.29 (0.98) ***	1.04 (0.63)	1.38 (0.85) ***	1.11 (0.67)	1.57 (0.85) ***
CRP mg/l, median (IQR)	1.90 (2.70)	2.20 (3.53) **	1.60 (2.20)	1.40 (2.10)	2.00 (3.20)	3.15 (5.65) ***	1.50 (2.10)	2.10 (3.30) *
BMI kg/m^2	26.4 (±3.7)	28.3 (±4.2) ***	27.0 (±3.7)	28.4 (±3.7) ***	27.0 (±4.9)	29.0 (±5.5) ***	26.8 (±4.0)	30.2 (±5.1) ***
Systolic BP mm Hg	142.9 (±20.6)	141.1 (±20.7)	144.1 (±20.3)	148.2 (±19.6) ***	142.2 (±21.0)	143.3 3 (±21.8)	143.3 (±20.2)	143.6 (±19.7)
Diastolic BP mm Hg	77.0 (±9.4)	74.7 (±10.8) **	74.4 (±9.7)	74.6 (±10.3)	72.6 (9.3)	70.5 (±10.5)*	71.6 (±10.2)	69.7 (±8.9)
Hypertension %[†]	73.5	88.7***	91.6	95.3	78.9	88.7**	92.5	95.8
Hypertensive medication %	50.0	75.2***	85.5	87.5	58.7	79.6***	84.6	90.5
Glucose lowering medication	-	46.1	-	64.1	-	36.6	-	64.2
CHD prevalence %[‡]	7.9	14.8**	71.1	59.4*	2.2	8.6***	34.4	24.2*
Family history MI %	30.1	39.1**	45.2	41.4	40.2	51.6**	56.7	53.7
Physical activity in midlife %	51.0	43.9	54.3	45.3	47.1	40.9	50.7	36.8*
Physical activity current %	39.6	27.4***	45.3	35.2*	31.3	26.3	34.2	16.8*
Education, more than secondary%	30.0	27.4	29.8	28.9	21.9	20.4	17.2	16.8
Smoking %	11.9	12.2	9.0	9.4	12.4	10.2	12.9	9.5
Haemoglobin A1c %	5.54 (±0.33)	6.38 (±0.88) ***	5.58 (±0.32)	6.55 (±0.79) ***	5.61 (±0.33)	6.32 (±0.95) ***	5.64 (±0.34)	6.58 (±0.88) ***
Glucose mmol/l	5.57 (±0.50)	7.95 (±2.09) ***	5.58 (±0.53)	7.92 (±2.19) ***	5.44 (±0.51)	7.60 (±2.00) ***	5.41 (±0.52)	7.97 (±2.38) ***

Significance estimates for age-adjusted comparison between those with and without T2D and not using statins (no) and statin users (yes): *p<.05; **p<.01; *** p<.001. [†]Hypertensive: systolic BP>140 mmHg, diastolic BP>90 mmHG or on hypertensive medication. [‡]Prevalence from history of MI, PCI, and CABG in hospital records.

Table 18. Prevalence of type 2 diabetes (T2D) and glucose lowering treatment in the AGES-Reykjavik study 2002-2006.

AGES-Reykjavik study	**Men**	**Women**	**Men and women**	**% of total T2D**
Total T2D at baseline % (n)	16.3 (358)	9.5 (281)	12.4 (639)	100
Diagnosed at study entry % (n)	5.1 (113)	2.8 (84)	3.8 (197)	31
With prevalent T2D at study entry % (n)	11.2 (245)	6.7 (197)	8.6 (442)	69
Mean T2D duration in years (±SD)			10.7 (±10.0)	
Glucose lowering treatment in prevalent T2D				
on special diet only % (n)	23.3 (57)	34.5 (68)		
on diabetic medication % (n)	76.7 (188)	65.5 (129)		
thereof using 1 drug % (n)	*43.7 (107)*	*40.1 (79)*		
" using 2 drugs % (n)	*25.7 (63)*	*19.8 (39)*		
" using 3 drugs % (n)	*6.9 (17)*	*4.6 (9)*		
" using 4 drugs % (n)	*0.4 (1)*	*1.0 (2)*		

persons with diagnosed diabetes were simultaneously taking 3 or 4 drugs for lowering blood glucose.

Effect of statins on cardiovascular and all-cause mortality

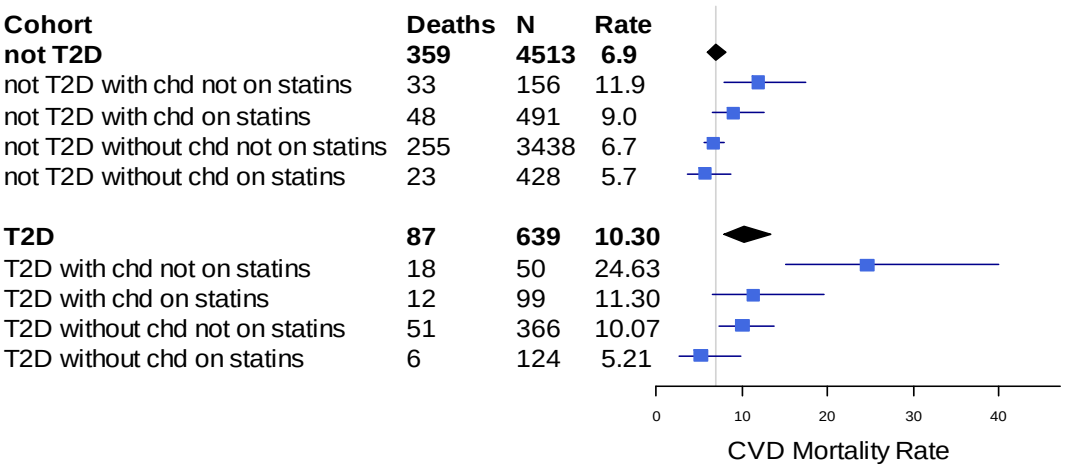
The five-year average cardiovascular disease mortality and all-cause mortality rates for those with and without diabetes are shown in Figure 6. Mortality rate is estimated according to statin use and prevalence of coronary heart disease, adjusted to age 75, sex and the mean levels of cardiovascular risk factors (cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, hypertensive medication and current smoking) within each cohort. About 26% of men and 16% of women without diabetes and about 35% in both sexes with diabetes were statin users. Statin medication was administered to 69.2% of persons with prevalent coronary heart disease and known diabetes compared to 31.6% of those with known diabetes but without coronary heart disease (Supplement, Table 1).

For individuals with diabetes and prevalent coronary heart disease, statin use was associated with a significantly lower rate of cardiovascular disease mortality (Figure 6a) compared to those not using statins, or 11.3 vs. 24.6 per 1000 person years. This amounts to 54% (95% confidence interval 14% to 75%) lower mortality rate in statin users. Similarly statin use was associated with an all-cause mortality rate of 27.8 vs. 63.3 per 1000 person years when comparing the same two groups (Figure 6b), amounting to 55% (31% to 71%) lower mortality rate in statin users. In individuals with diabetes but without coronary heart disease, the rate was 48% (1% to 73%) lower for cardiovascular disease mortality and 52% (26% to 69%) lower for all-cause mortality in the group using statins compared to non-statin users. Combining the groups the hazard of cardiovascular disease mortality was 50% lower in statin users compared to non-statin users and all-cause mortality was 53% lower (Supplement, Table 2).

Statin use was associated with 16% (-24% to 43%) lower mortality rate in individuals without diabetes as shown in Figure 6, albeit not statistically significant. For all-cause mortality statin users had 30% (11% to 46%) lower mortality rate than in non-statin users.

The effect of statins was not modified by the level of HbA1c, the use of oral hypoglycaemic or hypertensive medication, or whether the diabetes was prevalent or newly diagnosed (Supplement: Figure 1 and Figure 2).

a)



b)

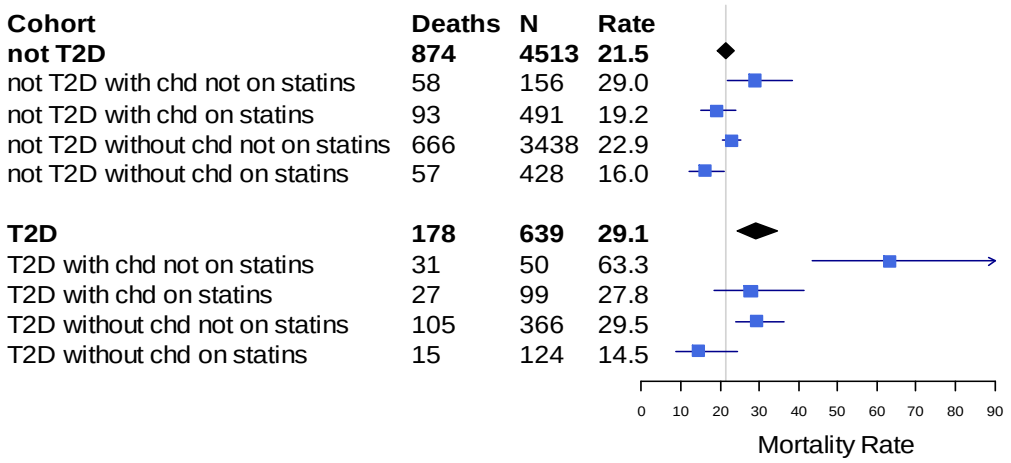


Figure 6. a) Cardiovascular disease (CVD) mortality rate and b) all cause mortality rate per 1000 person years for subjects without type 2 diabetes (not T2D) and with type 2 diabetes (T2D) according to statin use and prevalent coronary heart disease (chd). Rates have been adjusted to age 75, sex and the mean levels of cardiovascular risk factors (cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, hypertensive medication and current smoking) within each cohort. Follow up was through 2009 (a median period of 5.3 years) for the AGES-Reykjavik study. The vertical lines represent the mortality rate of all without diabetes (not T2D, N=4513).

An additional analysis of mortality rates with adjustment for current physical activity and education level did not result in different conclusions about the data. The adjusted mortality rates are shown in Supplement, Figure 3.

The dramatic effect of statin medication use on mortality rate in persons with diabetes is also reflected in the hazard ratios for the relative risk of cardiovascular and all-cause mortality in individuals with diabetes compared to those without as shown in Table 19. In persons with diabetes and prevalent coronary heart disease not on statins, the relative risk of dying from cardiovascular disease was 3.33 (2.05 to 5.50) when compared to those without diabetes, after adjusting for age, sex and cardiovascular risk factors. The individuals treated with statins, however, had a relative risk of 1.51 (0.83 to 2.75). In persons with diabetes but without coronary heart disease not on statins, the relative risk was 1.40 (1.03 to 1.89) compared to 0.71 (0.31 to 1.62) for those on statins. Adding CRP to the risk factor adjustment showed minimal attenuation of the hazard ratios (Table 19). This implies that the protective effect of statins is not solely attributable to the effect on these cardiovascular risk factors.

Table 19. Hazard ratios (HR) for the relative risk of cardiovascular disease (CVD) mortality and all cause mortality in people with type 2 diabetes (T2D) compared to all non-diabetics according to prevalent coronary heart disease (chd) and statin use*. The AGES-Reykjavik study from 2002-2006.

	Adjusted for age and sex		**Adjusted for age, sex, and †CVD risk factors**		**Adjusted for age, sex, †CVD risk factors and CRP**	
	HR	95% CI	**HR**	95% CI	**HR**	95% CI
Death from CVD						
All T2D	**1.71**	(1.35 to 2.17)	**1.48**	(1.15 to 1.90)	**1.45**	(1.13 to 1.86)
According to chd and statin use:						
T2D with chd not on statins	**4.71**	(2.93 to 7.58)	**3.33**	(2.02 to 5.50)	**3.20**	(1.94 to 5.29)
T2D with chd on statins	**1.92**	(1.08 to 3.43)	**1.51**	(0.83 to 2.75)	**1.55**	(0.85 to 2.82)
T2D without chd and not on statins	**1.53**	(1.14 to 2.05)	**1.40**	(1.03 to 1.89)	**1.34**	(0.99 to 1.82)
T2D without chd and on statins	**0.83**	(0.37 to 1.85)	**0.71**	(0.31 to 1.62)	**0.75**	(0.33 to 1.69)
Death from all causes						
All T2D	**1.44**	(1.22 to 1.69)	**1.35**	(1.14 to 1.61)	**1.32**	(1.11 to 1.57)
According to chd and statin use:						
T2D with chd not on statins	**3.48**	(2.43 to 4.99)	**2.88**	(1.98 to 4.18)	**2.72**	(1.87 to 3.95)
T2D with chd on statins	**1.61**	(1.10 to 2.37)	**1.34**	(0.90 to 1.99)	**1.37**	(0.92 to 2.04)
T2D without chd not on statins	**1.34**	(1.09 to 1.64)	**1.34**	(1.08 to 1.64)	**1.27**	(1.03 to 1.57)
T2D without chd on statins	**0.77**	(0.46 to 1.28)	**0.70**	(0.42 to 1.17)	**0,73**	(0.44 to 1.23)

*Individuals on statin medication are identified as on statins, those not on statin medication as not on statins.

†CVD risk factors: cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, hypertensive medication, and current smoking

5 DISCUSSION

The first aim of this thesis was to assess the long term effect of environmental and metabolic conditions on the risk of developing type 2 diabetes. While investigating the association of health and residency in the Reykjavik Study, a protective effect against later developing type 2 diabetes was observed in persons growing up in a rural area compared with living in urban Reykjavik from birth. This protective effect was greater in men than women and was reflected in all age groups. Differences between nutrition and physical activity of persons living in rural areas and urban Reykjavik while growing up, may explain the long term protective effect observed although life style and genetic variability may also account for some of these differences.

Based on glucometabolic status of participants in the first part of the AGES-Reykjavik study we analysed retrospectively the risk factor profiles in midlife of persons that developed type 2 diabetes in late life, and compared with those that maintained a normal glucose metabolism. The major finding was that persons with a family history of diabetes, elevated levels of fasting TG, BMI and systolic BP in midlife were at an increased risk of later developing type 2 diabetes. The modifiable risk factors (except TG in men) ascended from midlife values in all subgroups, but persons with type 2 diabetes had significantly higher values both in mid life and late life than others. This opens the possibility of predicting the risk of developing type 2 diabetes long before aberrations in glucose metabolism occur.

The second aim of our study was to examine the secular trend in mortality rate of older persons associated with cardiovascular disease and diabetes from 1993 to 2004. We observed decline in mortality rate both in those with and without diabetes, associated with reduced levels of modifiable cardiovascular risk factors and increased medical treatment. The excess mortality risk of persons with type 2 diabetes, however, persisted over the study period and was independent of cardiovascular risk factors. Marked improvement in survival of persons with type 2 diabetes was observed in association with statin medication and our results suggests that treatment with statins is of key importance for older persons with diabetes, regardless of the presence or absence of cardiovascular disease or the level of glucose or blood pressure control.

5.1 Long term risk of developing type 2 diabetes associated with early environment and metabolic profile in midlife

Data gathered in the Reykjavik Study gave us a unique opportunity to study the risk of developing type 2 diabetes according to early residency in rural, coastal or urban areas, if that might shed some light on the reason behind the low prevalence of the disease in Iceland. Our major finding was that risk of developing type 2 diabetes was 45% lower in men growing up in a rural area for the first part of their life before moving to urban Reykjavik compared to men living in Reykjavik from birth. In women the risk was 27% lower if they grew up outside Reykjavik. The risk associated with residing in different regions of the country for the first 20 years of life was also examined. We observed marked regional differences in the risk of developing type 2 diabetes and the lowest risk was found in persons coming from the rural regions in Eastern Iceland. When rural and coastal areas were combined the lowest risk was found in persons coming from the West and Northwest peninsula. There are number of possible explanations for this, such as environmental and social conditions that differed between regions, but there is also evidence for genetic isolates within the Icelandic population (Helgason et al., 2005) which may account for possible resistance to development of diabetes or increased susceptibility.

Food deprivation in rural areas in Eastern and Western Iceland as describes in various historical records may be also be an explanation. In addition we have nutritional recall data from the AGES-Reykjavik study showing a larger proportion of persons that grew up in rural areas reporting food deprivation while growing up compared with those growing up in Reykjavik (unpublished data, personal communication, J.E. Torfadottir). Of interest is the fact that this protective effect follows people throughout life long after they move to urban Reykjavik.

Data from Southeast Asia show lower prevalence of type 2 diabetes in rural areas than urban (Hussain et al., 2005; Misra et al., 2011; Ning et al., 2009; Pan et al., 2010; Ramachandran et al., 1992) and although food composition, climate and ethnicity is different in these places, the low prevalence in rural areas may reflect a low calorie content of the locally produced food along with heavier physical work load than in urban areas. In contrast are data from North America (Krishna et al., 2010) , Australia (Wan et al., 2008; Wan et al., 2007) and Poland (Lopatynski et al., 2001) where prevalence of diabetes is higher in rural areas than urban, partly explained by poorer socioeconomic factors. These studies compare contemporary rural and urban populations, but we have not found any studies showing a long

term protective effect of growing up in rural areas against developing type 2 diabetes long after migration to an urban area as illustrated in our data.

The effect of small size at birth and rapid growth after birth associated with increased risk of developing both coronary heart disease and type 2 diabetes has been studied quite extensively (Eriksson, 2007; Fernandez-Twinn & Ozanne, 2006; Forsen et al., 2000; Whincup et al., 2008), but no data are available on birth size in our cohort from rural areas. Cardiovascular risk factor levels in midlife were similar irrespective of residential area while growing up and our hypothesis is that difference in environmental conditions, both with respect to food composition and possible seasonal food deprivation, with more vigorous physical activity for those living in rural areas, may explain this protective effect. We postulate that a long lasting imprinting is caused by environmental conditions throughout the years of growing up, thus extending the fetal programming phenomenon (Hanson et al., 2011) to cover the time from birth to adulthood.

When examining retrospectively the association of risk parameters in midlife with glucometabolic status in late life we observed that already in midlife, more than a decade before type 2 diabetes was diagnosed, family history, high levels of BMI, TG and systolic blood pressure were associated with persons later developing type 2 diabetes. Family history of diabetes is a well-known risk factor (Valdez, 2009) and short term prediction studies have shown that high BMI and high systolic blood pressure along with high blood glucose are risk factors for type 2 diabetes, but high TG levels have not been greatly emphasized until recently as an important risk predictor (Alberti et al., 2006; Brunzell et al., 2008; Ryden et al., 2007). Diabetic hypertriglyceridemia has been studied extensively for a long time (Reaven et al., 1975; Taskinen, 2001), but using it as a prediabetic risk factor is more novel. Our data show that persons at risk could be identified much earlier, long before any disturbances in glucose metabolism are measurable, based on levels of the three modifiable risk parameters observed, TG, BMI and systolic BP as suggested in our findings. After identification persons at risk could be monitored more closely thereafter and possibly directed towards lifestyle modifications, thus hopefully delaying the onset of type 2 diabetes (Knowler et al., 2002; Tuomilehto & Lindstrom, 2003).

In a recent systematic review a summary of 43 papers with 94 risk models or scores for identifying persons at risk of developing type 2 diabetes were reported (Noble et al., 2011). These risk models varied greatly and used from 3 to 14 components, but triglycerides were not mentioned specifically in any. A few, however, were also studying atherosclerosis risk in

communities and therefore included lipids in their risk models and the Tehran Lipid and Glucose Study risk score is an example. They used triglyceride HDL-cholesterol ratio along with systolic blood pressure, family history of diabetes, waist-to-height ratio and fasting plasma glucose (Bozorgmanesh et al., 2011) and their model discriminated subjects with substantial risk for diabetes, appreciably better than 2-hours post-challenge plasma glucose alone. According to Noble the balance of research efforts is now shifting from devising new risk scores to exploring how best to use those we already have. Still there is scope for improving and adapting the most appropriate risk score for each health care region in light of local findings and practices.

5.2 Low prevalence of type 2 diabetes in Iceland

The prevalence of type 2 diabetes estimated in the first stages of the Reykjavik Study was 3.6% at the mean age of 53 years as seen in paper I. The prevalence increased with age and was 12% in the last stage of the Reykjavik Study at the mean age was 75 years, the same as in the AGES-Reykjavik cohort at the mean age of 77 years, examined over a decade later (paper III). This is low for the age group 70-87 years, compared with prevalence of over 20% in adults older than 65 years in the United States (Harris et al., 1998; Selvin et al., 2006). In the AGES-Reykjavik study during 2002-2006, of those with type 2 diabetes 69% had already been diagnosed but 31% were diagnosed at entry, showing an improved medical attention compared with the last stage of the Reykjavik Study from 1991-1996, when 41% had known diabetes and 59% were diagnosed at study entry. The duration of disease was about 10 years in both cohorts when entering the studies. During 1999-2003 a survey from the US found 31% of persons with type 2 diabetes undiagnosed in the community (Selvin et al., 2006). As we base our diagnosis of unknown diabetes at entry on a single measurement of fasting glucose we may have overestimated the numbers, both in the AGES-Reykjavik and the Reykjavik studies (Selvin et al., 2007).

Men in the AGES-Reykjavik study show both higher prevalence and receive more intensive glucose lowering treatment judged from the medication profile of hypoglycaemic drugs than women and similar observations have been reported from the Icelandic diabetic clinics (Bjornsdottir et al., 2004). In the DECODE study from 13 European countries (DECODE, 2003) the prevalence of diagnosed diabetes did not differ between men and women except in people over the age of 80 years where the prevalence in women was higher.

When compared with prevalence of diabetes in Europe, Icelanders are shown to be at the lower end of the scale (DECODE, 2003; Forouhi et al., 2006).

In paper II the glucometabolic status was also assessed by mean values of fasting serum insulin along with calculated $HOMA_{IR}$ and HbA_{1c} and metabolic syndrome criteria were estmated. The highly significant difference found in fasting insulin levels and $HOMA_{IR}$ between the groups with normal glucose levels and those with impaired glucose regulation clearly show that insulin resistance was already well established in persons with IFG. The stepwise increase observed in HbA_{1c} values, when comparing persons with IFG and type 2 diabetes with the control group illustrated the gradual impairment in glucose regulation. The metabolic syndrome reflected differences in risk parameters between the three groups, showing about 60% of persons with type 2 diabetes and almost 50% of those with IFG with 2 or more metabolic syndrome criteria (Alberti et al., 2006), compared to 25% of persons with normal glucose metabolism.

In a review of prospective studies from July 1998 through August 2004 Ford concluded that the population-attributable fraction for the metabolic syndrome, as it was currently conceived, was approximately 6-7% for all-cause mortality, 12-17% for cardiovascular disease, and 30-52% for diabetes (Ford, 2005). Later in a meta-analysis of 16 cohort studies Ford and co-workers concluded the metabolic syndrome, however defined, had a stronger association with incident diabetes than previously demonstrated for coronary heart disease (Ford et al., 2008). They further concluded its clinical value for diabetes prediction remained uncertain as limited evidence suggested that fasting glucose alone may be as good as the metabolic syndrome for diabetes prediction. In light of current evidence we have put stronger emphasis on individual risk factors rather than the metabolic syndrome in other part of this thesis.

Prevalence of type 2 diabetes in Iceland has been increasing in the age group 45-64 over the last decades and had reached 6% in men and 3% in women in 2007; this coincides with increasing body mass index. The prevalence has doubled in men since 1967 and increased by 50% in women (Sigurdsson et al., 2008; Thorsson et al., 2009) so we can expect increased prevalence in the older population in coming years. Still it is low compared with our neighbouring countries and may reflect a gradual development from the extremely low prevalence seen in the first half of the 20^{th} century (Albertsson, 1953) in Iceland.

5.3 Cardiovascular morbidity and mortality associated with type 2 diabetes

Cardiovascular disease is strongly associated with diabetes and is one of the more severe co-morbidities of the disease. CRP is a biomarker for low systemic inflammation and one of the cardiovascular risk factors, but has recently also been linked to type 2 diabetes, more so in women than in men (Dehghan et al., 2007). In paper II we observed that men developing IFG or type 2 diabetes did not report significantly higher prevalence of CVD than those with normal glucose metabolism, nor did they have higher levels of CRP. Women with type 2 diabetes, however, reported significantly higher CVD prevalence ($p<0.05$) and had higher CRP levels than women with normal glucose metabolism. This may reflect a higher level of systemic inflammation, possibly associated with high BMI (Eiriksdottir et al., 2009). In men with normal glucose metabolism prevalence of CVD was 100% higher than in women, but only 50% higher in diabetic men compared with diabetic women. The explanation may be that men in our study with the most severe CVD and type 2 diabetes have not survived or were unable to attend. Others have shown, however, that diabetes has a greater impact on CHD mortality risk in women than in men (Carnethon et al., 2010; Natarajan et al., 2005) and in a meta-analysis of 37 prospective cohort studies diabetic women had a 50% higher relative risk for fatal coronary heart disease than diabetic men (Huxley et al., 2006). Only 2 of the 37 studies, however, were published after year 2000 and a possible explanation given for the different outcome between the sexes was that women had more adverse cardiovascular risk factor profiles and did not receive the same intense medical treatment as men. Information from hospital records (paper III) showed that men with diabetes had a higher CHD prevalence than those without, or 32% versus 25% and women 14% versus 8%, again showing that men with diabetes had 2.3 times higher prevalence than women and in those without diabetes the ratio was 3.1, illustrating that men with diabetes fare worse than women in our study.

In paper III we studied secular trend in cardiovascular mortality from the Icelandic National Roster (StatisticsIceland, 2010). When comparing the two cohorts of older persons, the Reykjavik Study in 1993 and AGES-Reykjavik in 2004, we observed a decline of 32% in cardiovascular mortality rate between the studies. The decline in this age group is equivalent to the decline in the population at large in Iceland (StatisticsIceland, 2010) and in harmony with the decline in cardiovascular mortality risk in the Western World over the last decades (Ford et al., 2007; Hughes et al., 2012; Kesteloot et al., 2006; Unal et al., 2005). In an attempt to evaluate the contribution of changes in risk factor levels in this decline in mortality we adjusted for mean levels of risk factors and medical treatments across the two cohorts and

obtained attenuation in the estimate of cardiovascular mortality from 32% to 25%. Thus the change can only partly be due to reduction in cardiovascular risk factors and improved medical treatment and remains to be fully explained. Improved general living conditions could be a causal factor but it is possible that reduced risk factor burden has benefitted younger people to a larger degree than the older population who lived through higher risk factor levels in their prime years, emphasising the importance of life long risk burden in the development of non-communicable disease.

Another finding related to the decline in mortality was the increase in prevalent coronary heart disease, obtained from hospital records, seen between the two time periods both in those with and without diabetes. Most likely this can be explained by increased survival rate in coronary heart disease patients, following the favourable changes in cardiovascular risk factor levels in all age groups, that would have benefitted the participants in the AGES-Reykjavik study to a greater degree than the cohort in the last stage of the Reykjavik Study. An increase in medical intervention has also had an effect in reducing premature deaths from coronary heart disease, especially from myocardial infarction, as was observed in Iceland (Aspelund et al., 2010) during the time period 1981 to 2006.

Cardiovascular and all-cause mortality rates declined similarly both in those with and without type 2 diabetes. The decline in mortality rates was greater in individuals with diabetes than those without, albeit not statistically significant. As a result a decline was also observed in the age and sex adjusted hazard ratio of cardiovascular mortality between 1993 and 2004 when individuals with diabetes were compared with those without, but again the decline did not reach statistical significance. After adjustment for cardiovascular risk factors and medical treatment the observed attenuation in hazard ratios did not alter the trend in hazard ratio reduction between the two time points. Although persons with diabetes benefitted at least equally from improved conditions as those without diabetes the increased mortality risk of persons with type 2 diabetes persisted over time, and was independent of both cardiovascular risk factors and medical treatment.

5.4 Statin medication in cardiovascular disease and type 2 diabetes

In the last part of our study (paper IV) we found a marked reduction in both cardiovascular and all-cause mortality associated with statin medication, especially in persons with type 2 diabetes. In persons with diabetes this mortality rate reduction was independent of prevalent

coronary heart disease or glucose-lowering treatment, reducing the mortality rate in individuals with diabetes to a level comparable to those without diabetes.

Statin medication in diabetes has increased gradually during the last decade. Data from the U.K. General Practice Research Database showed an increase in statin use from about 5% in 1996 to 63.5% in women and 71.0% in men in 2005 (Charlton et al., 2008), which was associated with decline in mortality of 26% in women and 47% in men in the first two years following diagnosis of diabetes. The authors concluded that widespread implementation of more effective medication in lowering lipid levels, glucose and blood pressure may have contributed to this effect.

Similarly, in Denmark, only 7% of patients receiving glucose-lowering medication also received statins in 1997, but this had increased to 62% in 2007 (Dominguez et al., 2009), information on changes in mortality was not available. In our cohort of older persons with diabetes the prevalence of statin medication use was 35% overall. In those with known diabetes but without coronary heart disease the prevalence of statin medication use was 31.6%, but 11.6% in the newly diagnosed without coronary heart disease.

In recent years there has been a steady increase in statin use in Iceland (Sigurdsson et al., 2008) and an greater awareness of the importance of statin use in diabetes has been experienced, although no published data are available to illustrate that. In the Icelandic clinical guidelines for the treatment of type 2 diabetes from the Directorate of Health (Bjornsson et al., 2009) use of statin medication to treat to lipid targets is advised. Therefore we would expect to day that more old people with diabetes are on statin medication than we saw in the AGES-Reykjavik study.

There is ample evidence coming from clinical trials to support the use of statin treatment in diabetes as advised in clinical guidelines (Collins et al., 2003; Kearney et al., 2008; Matikainen et al., 2010) and the beneficial effect of statins is most likely due to favourable impact on vascular event rates both in those with and without diabetes. In the Heart Protection Study (Collins et al., 2003) for example it was concluded that 40 mg of simvastatin daily would probably reduce the rate of first major vascular event by about a third. Similarly a two-year treatment period with atorvastatin in type 2 diabetes in the CARDS study reduced the death rate by 27%, prompting an early termination of the trial (Colhoun et al., 2004). The authors concluded that lipid-lowering treatment should at least receive the same attention as glycemic and blood pressure control in type 2 diabetes patients without a history of cardiovascular disease, which is in harmony with current clinical guidelines. Aggressive

multifactorial treatment of high-risk individuals with type 2 diabetes has been shown to be important (Gaede et al., 2008), and may also be appropriate for persons diagnosed above the age of 70. Recent results from several large studies (Duckworth et al., 2009; Gerstein et al., 2008), however, have indicated that caution may be needed as regards aggressive glucose lowering treatment in persons with long-established coronary heart disease and diabetes of long duration. In our study, statin use at baseline, but not use of glucose-lowering medication, is associated with the marked reduction in cardiovascular and total mortality rate, reducing mortality in persons with diabetes to a level similar to those without diabetes. Our data also showed a beneficial effect of statin use irrespective of lipid levels and thus support the argument for "individualised or personalised care" of patients at risk relaying both on the best predictors and factors that reduce risk, put forward by Hayward and co-workers (Hayward et al., 2006; Hayward & Krumholz, 2012; Hayward et al., 2010).

Recently in a collaborative meta-analysis of 102 prospective studies (Sarwar et al., 2010) demonstrated that the increased cardiovascular mortality seen in type 2 diabetes is not explained by conventional cardiovascular risk factors. This suggests that the effect of the statins on cardiovascular mortality seen in our population-based cohort may reach beyond the statins' effect on lowering cholesterol levels, possibly by reducing the damaging effect of inflammatory agents (Ridker et al., 2009; Sever et al., 2005). Inflammation as measured by CRP, however, does not appear to be the explanation in our study, as adjusting for CRP in the risk models did not attenuate the relative risk although those on statins had markedly lower CRP. This warrants further study.

In randomised clinical trials statin medication, under the rigors of controlled study conditions in selected individuals, has been shown to be helpful (Brugts et al., 2009; Collins et al., 2003; Kearney et al., 2008). In our study we have shown that statin medication also is very likely to be important in older persons in the community, persons which may or may not fit the stringent criteria of normality imposed for inclusion into randomized clinical trials.

5.5 Strengths and limitations

The Reykjavik Study and Age, Gene/Environment Susceptibility - Reykjavik Study are two large and comprehensive population-based observational studies that enable us to reach valuable epidemiological information about the health status of the Icelandic population. The participation rate of 71% in the Reykjavik Study is high with a proportionally large national

representation. In the AGES-Reykjavik study the participation rate of 75% among men and 68% for women is also high and the nonparticipants when asked, stated they did not feel up to attending. Midlife data show that nonparticipants had a higher mean value of systolic blood pressure (men 143 vs. 136 and women 133 vs. 127 mmHg), but similar values in glucose, BMI and TG (Harris et al., 2007).

A weakness in our study is the use of a single fasting glucose level for the diagnosis of type 2 diabetes and IFG at study entry, leading to possible misclassification of glucometabolic impairment. Although the majority of epidemiological studies rely on a single estimation of fasting glucose level it has been shown by using a mean of two fasting glucose levels taken two weeks apart that only a 70% repeatability may be expected (Selvin et al., 2007). In the collaborative meta-analysis of fasting blood glucose and risk of vascular disease (Sarwar et al., 2010) a moderate association of impaired fasting glucose status with coronary heart disease and stroke was shown. By contrast total cholesterol and systolic blood pressure each showed a stronger and nearly log-linear associations with vascular risk.

A second limitation is the unavailability of dietary information for this analysis leaving us to relay on indirect data in paper I. Lack of data on the prevalence of type 2 diabetes in present rural areas in Iceland may also be considered a weakness.

It would have been of value to compare mortality rate between men and women in papers III and IV but the low number of deaths during the follow up time lead to a large uncertainty that made comparison impractical.

6 CONCLUSIONS

The main conclusions that can be drawn from the studies presented are the following:

Living in a rural area for the first 20 years of life protected against development of type 2 diabetes later in life even after living in urban Reykjavik for over 30 years. The difference in environmental conditions, both with respect to food composition with possible seasonal food deprivation and physical activity in adolescence may explain this protective effect. It is postulated that a long lasting imprinting is caused by environmental conditions throughout the years of growing up.

Family history of diabetes, high levels of BMI, TG, and high systolic blood pressure in midlife are associated with the development of IFG and type 2 diabetes in late life. Our data show a continued rise in these risk parameters over the study period opening a possibility of predicting the risk of developing type 2 diabetes decades before onset. The campaign for health promotion and prevention strategies might accordingly start quite early in life in the hope of preventing or delaying development of type 2 diabetes and its detrimental effect on cardiovascular health.

We observed a secular decline in mortality rate from cardiovascular disease and from all causes in two cohorts of older persons with and without type 2 diabetes studied eleven years apart, between 1993 and 2004. Concurrently decrease in major cardiovascular risk factor levels along with improved medical treatment was observed. Type 2 diabetes, however, still persists as an independent risk factor for cardiovascular mortality through as yet unknown mechanisms.

Statin use, irrespective of glucose-lowering and antihypertensive medication, eliminates the difference in the mortality rate of older persons with type 2 diabetes, compared to those without diabetes. Our study suggests that treatment with statins is paramount in the multifaceted management of type 2 diabetes and is therefore of key importance for older persons with diabetes, regardless of the presence or absence of cardiovascular disease or the level of glucose or blood pressure control.

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