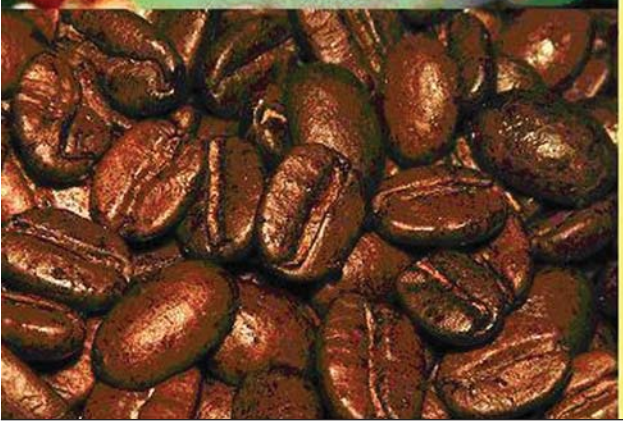

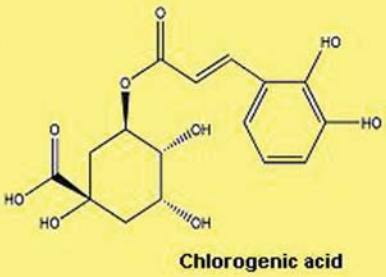

Siamak Bidel

Coffee and Risk of Type 2 Diabetes

Publications of the National Public Health Institute A 18/2008

Department of Health Promotion and Chronic Disease Prevention
National Public Health Institute
and
Department of Public Health
Faculty of Medicine
University of Helsinki

Helsinki, Finland 2008

Siamak Bidel

COFFEE AND RISK OF TYPE 2 DIABETES

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine, University of Helsinki, for public examination in the Helsinki University Museum Arppeanum, Snellmaninkatu 3, on Jun 18, 2008, at 12 o'clock noon.

Diabetes Unit
Department of Health Promotion and Chronic Disease Prevention,
National Public Health Institute
&
Department of Public Health,
Faculty of Medicine
University of Helsinki
Helsinki, Finland
2008

Publications of the National Public Health Institute KTL A18 / 2008

Julkaisija-Utgivare-Publisher

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ISBN 978-951-740-834-9
ISSN 0359-3584
ISBN 978-951-740-835-6 (pdf)
ISSN 1458-6290 (pdf)

Yliopistopaino
Helsinki 2008

To my Wife and sons

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Siamak Bidel, Coffee and risk of type 2 diabetes,
Publications of the National Public Health Institute, A18/2008, 83 Pages
ISBN 978-951-740-834-9; 978-951-740-835-6 (pdf-version), ISSN 0359-3584; 1458-6290 (pdf-version)
http://www.ktl.fi/portal/4043

ABSTRACT

Type 2 diabetes is one of the diseases that largely determined by lifestyle factors. Coffee is one of the most consumed beverages in the world and recently released data suggest the effects of coffee consumption on type 2 diabetes. The objective of the present study was to evaluate the effects of habitual coffee consumption on various aspects of type 2 diabetes and its most common complications.

This study is part of the national FINRISK studies. Baseline surveys were carried out between 1972 and 1997. The surveys covered two eastern regions in 1972 and 1977, but were expanded to include a third region in southwestern Finland in 1982, 1987, 1992, and 1997. The Helsinki capital area was included in the survey in 1992 and 1997 and the Oulu province, in northern Finland, in 1997. Each survey was drawn from an independent random sample of the national register of subjects aged 25-64. In 1997, an additional sample of subjects aged 65-74 was conducted.

The blood pressure, weight, and height of subjects were measured. By using self-administered questionnaires data were collected on medical history, socioeconomic factors, physical activity, smoking habits, and alcohol, coffee, and tea consumption.

Higher coffee consumption was associated with higher body mass index, occupational physical activity and cigarette smoking, and lower blood pressure, education level, leisure time physical activity, tea consumption and alcohol use.
Age, body mass index, systolic blood pressure and current smoking were positively associated with the risk of type 2 diabetes, however, education, and occupational, commuting and leisure time physical activity were inversely associated.

The significant inverse association between coffee consumption and the risk of type 2 diabetes was found in both sexes but the association was stronger in women. Coffee consumption was significantly and inversely associated with fasting glucose, 2-hour plasma glucose, fasting insulin, impaired fasting glucose, impaired glucose regulation, and hyperinsulinemia among both men and women and with isolated impaired glucose tolerance among women.

Serum γ-glutamyltransferase modified the association between coffee consumption and incident diabetes. Among subjects with high serum γ-glutamyltransferase ($\geq 75^{th}$ percentile), coffee consumption showed an inverse association for women, as well as men and women combined.

An inverse association also occurred between coffee consumption and the risk of total, cardiovascular disease, and coronary heart disease mortality among patients with type 2 diabetes.

The results of this study showed that habitual coffee consumption may be associated with a reduced risk of type 2 diabetes. Coffee consumption may have some effects on several markers of glycemia, and may lower the incident of type 2 diabetes in high normal serum γ-glutamyl-transferase levels. Total, cardiovascular disease, and coronary heart disease mortality rate among subjects with type 2 diabetes may also be reduced by coffee consumption.

Keywords: Coffee, Diabetes mellitus type 2, Risk factors, Cardiovascular diseases, Coronary disease, Health surveys

CONTENTS

ORIGINAL PUBLICATIONS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by their Roman (I-V):

I Tuomilehto J, Hu G, Bidel S, Lindström J, Jousilahti P. Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. ***JAMA*** **2004; 291:1213-1219**

II Bidel S, Hu G, Sundvall J, Kaprio J, Tuomilehto J. Effects of coffee consumption on glucose tolerance, serum glucose and insulin levels- A cross sectional analysis ***Horm Metab Res*** **2006; 38: 38-43**

III Hu G, Jousilahti P, Peltonen M, Bidel S, Tuomilehto J. Joint association of coffee consumption and other factors to the risk of type 2 diabetes: a prospective study in Finland. ***Int J Obes*** **2006; 30:1742-1749**

IV Bidel S, Silventoinen K, Hu G, Lee D-H, Kaprio J, Tuomilehto J. Coffee consumption, serum gamma-glutamyltransferase and risk of type II diabetes. ***Eur J Clin Nutr*** **2008; 86:178-185**

V Bidel S, Hu G, Qiao Q, Jousilahti P, Antikainen R, Tuomilehto J. Coffee consumption and risk of total and cardiovascular mortality among patients with type 2 diabetes. ***Diabetologia*** **2006 49:2618-2626**

ABBREVIATIONS

ANOVA	univariate analysis of variance
BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
GGT	γ-glutamyltransferase
GIP	gastric inhibitory polypeptide
Glc-6-Phase	glucose-6-phosphatase
GLP-1	glucagon-like peptide-1
GSH	Glutathione
HRs	hazards ratios
Mg	magnesium
MONICA	MONItoring trends and determinants in CArdiovascular disease
OGTT	oral glucose tolerance test
OR	odds ratios
WHO	World Health Organization

1. INTRODUCTION

There is no doubt that coffee is one of the most desired and consumed beverages in the world and Finns seems to partake the most with 11.6 kg per capita, while the European average is 5 kg (Figure 1) (International Coffee Organization (ICO) 2007). Why did coffee become so popular, and fulfill a "progressive" social function? The most probable answer might be in the rapid prominent stimulant effect of coffee for increasing alertness; even the actual aroma and smell of fresh brewed coffee would be enough to start stimulation in coffee drinkers!

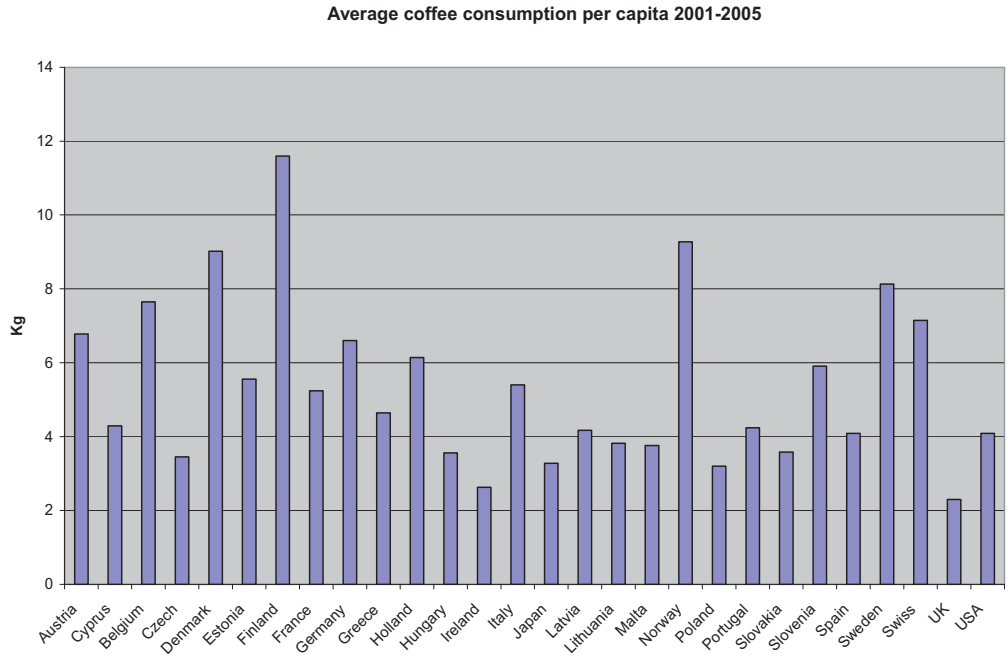


Figure 1. Average coffee consumption based on the data from ICO.

During the recent decades, research has attempted to evaluate the harms or benefits received from coffee. Knowledge on both the positive and negative health effects of coffee is important; it allows individuals to make informed choices regarding coffee consumption. The potential health effects of coffee and caffeine have been studied through epidemiological, clinical, and experimental research. The psychoactive effects of caffeine have been well documented, and the effects of coffee are considered synonymous with those of caffeine. Even though other, more abundant components of coffee, may also have many biological effects but may have not yet been extensively studied.

In fact, coffee is a complex mixture of potential physiologically active chemicals. Coffee's chemical composition is determined by a complex interaction of agricultural factors, roasting, blending, and brewing. Other than caffeine, coffee is the major source of phenolic polymers and chlorogenic acid (Clifford 2000; Herrmann et al. 1976; Kuhnau 1976) which is believed to possess antioxidant activity and possibly useful in healing or preventing diseases. The most prevalent phenolic compounds in food are hydroxycinnamic acids (Manach 2003; Herrmann et al. 1976; Kuhnau 1976). A major component of this class is caffeic acid, which occurs in food mainly as esters called chlorogenic acid (Clifford 2000). Although compounds with antioxidant properties (mainly chlorogenic acid) are lost during the roasting of coffee beans (Parliament et al. 2000), the overall antioxidant activities of coffee brews can be maintained, or even enhanced, by the development of compounds possessing antioxidant activity (Shearer et al. 2003).

Type 2 diabetes is the most common form of diabetes and a major health problem, associated with excess morbidity and mortality, resulting in substantial health care costs. It is caused by a complicated interplay between genes and environment. The environmental factor such as obesity is an absolute risk for developing type 2 diabetes, but many obese individuals are not diabetic and many type 2 diabetes cases occur among non-obese people. It demonstrates that genetic factors may play an important role in developing type 2 diabetes, but the pattern might be complicated, involving multiple genes and multiple gene-environment interactions.

Type 2 diabetes is a progressive, life-long condition that increases the risk for many serious complications such as cardiovascular disease, retinopathy, neuropathy, and nephropathy. This chronic condition is characterized by the development of both microvascular and macrovascular complications. These complications, accounts for most of the increased morbidity and mortality associated with type 2 diabetes (Kannel and McGee 1997; Nathan 1993; Stamler et al. 1993; Manson et al. 1991; Fuller et al. 1983). The costs of diabetes care are mostly attributed to the long term complications. New guidelines however have revealed that changing the lifestyle and dietary behavior can prevent, or delay, the development of the disease and its complications as well.

This study describes the association of habitual coffee consumption with developing type 2 diabetes among individuals in Finland. The study examined the association between coffee consumption and different parameters of glucose metabolism. The interaction between serum γ-glutamyltransferase (GGT) and coffee consumption on the risk of type 2 diabetes has been assessed and the effects of coffee consumption on the risk of total and cardiovascular disease (CVD) mortality among patients with type 2 diabetes has also been evaluated.

2. REVIEW OF THE LITERATURE

2.1 *Definitions and classification of type 2 diabetes*

Appropriate classification is major requirement for orderly epidemiologic and clinical research on and management of diabetes mellitus. Furthermore, a hallmark in the process of understanding the etiology of a disease and studying its natural history is the ability to identify and differentiate its various forms and place them into a rational etiopathologic framework. While a number of nomenclature and diagnostic criteria have been proposed for diabetes, no systematic categorization existed until just two decades ago. Now diabetes mellitus is recognized as being a syndrome, a collection of disorders that have hyperglycemia and glucose intolerance as their hallmark, due to either insulin deficiency or to the impaired effectiveness of insulin's action, or a combination of these.

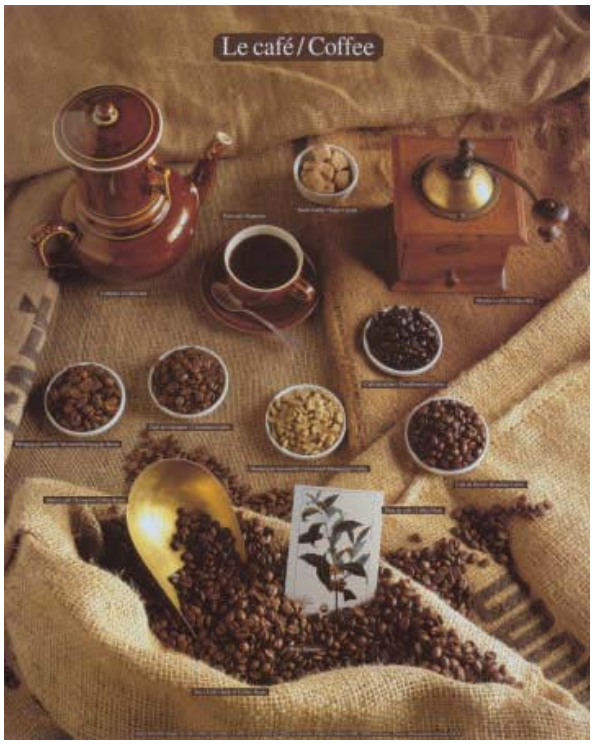
Type 2 diabetes, formerly known as non-insulin-dependent diabetes, is the most common form of diabetes and a major health problem associated with excess morbidity and mortality and results in substantial health care costs. In western countries, it constitutes approximately 90% of all diabetes cases. In certain populations such as North American Indians and in the South Pacific regions, it is virtually the only form of diabetes (Zimmet et al. 1990). The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (Wild et al. 2004). In Europe, their number will increase from approximately 16 million in 1994 to 24 million in 2010 (Amos et al. 1997).

In contrast to Type 1 diabetes or insulin dependent diabetes mellitus, patients with type 2 diabetes are not dependent on exogenous insulin for the prevention of ketonuria. They may, however, require insulin for the correction of hyperglycemia if this cannot be achieved through diet or oral anti diabetic agents. Most patients diagnosed with type 2 diabetes are adults, but the disease may also occur in young people not requiring insulin. In addition, the age at diagnosis of type 2 diabetes tends to be much younger in high prevalence groups (French et al. 1990). Consequently, age at onset is not recommended as a determinant of whether a patient should be classified as type 2 diabetic and the terms "adult-onset" and "maturity-onset" diabetes are no longer in use.

Type 2 diabetes is caused by a complicated interplay between genes and environment. Genetic factors play an important role in type 2 diabetes, but the pattern is complicated, since both impairment of beta cell function and abnormal response to insulin are involved.
During the past decade, plenty of efforts have been devoted to exploring type 2 diabetes genes. These genes encode proteins strongly linked to diabetes (Sandhu et al. 2007; Winckler et al. 2007; Gudmundsson et al. 2007; Florez et al. 2004;Nielsen et al. 2003; Gloyn et al 2003; Altshuler et al. 2000; Horikawa et al. 2000). For instance, defective genes that regulate a molecule called peroxisome proliferator-activated receptor gamma (PPARγ) may contribute to type 2 diabetes in some patients. It regulates adipocyte differentiation and lipid and glucose metabolism (Altshuler et al. 2000; Auwerx 1999). Geneticists have also identified genes that

were mutated in diabetic patients (Gloyn et al. 2004; Barroso et al. 1999; Nishigori et al. 1998; Inoue et al. 1998) and genes that are targets of anti diabetic therapies (Nielsen et al. 2003; Altshuler et al. 2000).
A strong genetic basis of the disease is evidenced by the frequent familial pattern of occurrence, its high prevalence in certain ethnic groups, and genetic admixture studies. Studies on identical twins have been particularly important in establishing the influence of genetic factors in the etiology of type 2 diabetes. Most of the co-twins of people with type 2 diabetes develop the disease themselves, but discordance indicates that environmental factors are also involved in the etiology (Kaprio et al. 1992; Newman et al. 1987). A large Finnish twin cohort study found the heritability of type 2 diabetes to be about 79% (Kaprio et al. 1992).
Dramatic changes in the prevalence or incidence of type 2 diabetes have been observed in communities where major changes have occurred in the type of diet consumed, from a traditional indigenous diet to a typical western diet, e.g. Pima Indians in Arizona, Micronesians in Nauru and Aborigines in Australia (Lako et al. 2001; Bennett 1999; Hetzel and Michael 1987).
Changing disease rates are almost explained by changes in several dietary factors as well as by changes in other lifestyle related factors (obesity and sedentary lifestyle). This may be particularly important in triggering the genetic elements that cause this type of diabetes.

Type 2 diabetes is characterized by the progressive development of the microvascular and macrovascular complications. These complications, and in particular atherosclerotic lesions, are the main causes for most of the increased morbidity and mortality in type 2 diabetes and the people with the disease are at much higher risk of fatal ischemic heart disease and stroke (Kannel and McGee 1997; Nathan 1993; Stamler et al 1993; Manson et al. 1991; Fuller et al. 1983).
In general, type 2 diabetes increases the risk of CVD mortality to about 3-fold compared with non-diabetic subjects. The progression of atherosclerosis in diabetes is probably the result of the other major risk factors which are more prevalent in diabetics. Obesity and dyslipidemia, the derangement in carbohydrate metabolism (hyperglycemic environment, hyperinsulinism, and insulin resistance), a prothrombotic tendency, microalbuminuria, and hypertension are some of these factors (Stevense et al. 2004; Knight 2003; Pastor-Barriuso et al. 2003; Resnick and Howard 2002; Tooke 2000; Harris and Eastman 1998). The costs of diabetes care are mostly attributed to the long term complications.



2.2 *Coffee*

The word coffee is derived from the name of the province Keffa where, prior to 1000 A.D., goatherds from Abyssina/Ethiopia discovered the strange effect of wild coffee beans on the goats.

Seven centuries after this accidental discovery, coffee's restorative power was well known and coffee spread throughout the neighboring countries, mostly Arabic Islamic countries. About 200 years later coffee entered to the Europeans life and was thoroughly accepted as a new beverage (National Geographic Society 1999). Now, coffee is one of the most consumed beverages in the world and while a great number of its constituents have been recognized, a better understanding of their actual effects on human health and metabolism is greatly desired.

2.2.1 *Chemical Composition of Coffee*

Although coffee has been consumed for centuries, the chemical composition of coffee is not completely known. Coffee is a complex mixture of more than a thousand chemical components determined by a complex interaction of agricultural factors, roasting, blending, and brewing. The water soluble constituents are: phenolic polymers (pulp) 8%, polysaccharides 6%, chlorogenic acids 4%, minerals 3%, water 2%, caffeine 1%, organic acids 0.5%, sugars 0.3%, lipids 0.2%, and aroma 0.1% (Institute for Coffee Studies 2001).
According to phytochemical database (Agricultural Research Service 2007), unroasted, green coffee seeds contain the following soluble compounds:

2,3,5-TRIMETHYLPHENOL,
2-ETHYLPHENOL
2-METHOXY-4-ETHYLPHENOL
2,4-METHYLENEPHENOL
DICAFFEOYL-QUINIC ACID
4-ETHYLPHENOL
4-METHOXY-4-VINYLPHENOL
ACETALDEHYDE
CAFFEINE
CAFFEOL
CAFFEOYL-3-QUINIC ACID
CAFFETANNIC ACID
CHLOROGENIC ACID
CITRIC ACID
DATURIC ACID
GUAIACOL
HYPOXANTHINE
ISOCHLOROGENIC ACID
PUTRESCINE
SCOPOLETIN
SPERMIDINE
SPERMINE
SUGARS
TANNIC ACID
TANNIN
THEOBROMINE
THEOPHYLLINE
THIAMIN
TRIGONELLINE
XANTHINE

Some of the coffee's compounds are more involved in human health and/or better documented in previous literature. Caffeine and chlorogenic acid are two of them.

Caffeine

Caffeine or 1,3,7-trimethylxanthine is a natural purine alkaloid in coffee beans. It is probably the most frequently ingested pharmacologically active substance in the world (Nawrot et al. 2003). After the ingestion of caffeine, it is rapidly and almost completely absorbed in the stomach and early parts of the intestine, and then distributed to all parts of body. Caffeine metabolism takes place in the liver by cytochrome P450 isoform (CYP1A2). Almost 95% of caffeine is metabolized through this pathway resulting in the formation of 1,7-dimethylxanthine (paraxanthine). The final product of destabilization will be 5-acetylamino-6-amino-3-methyluracil (figure 1) (Crews et al. 2001; Krul and Hageman 1998).

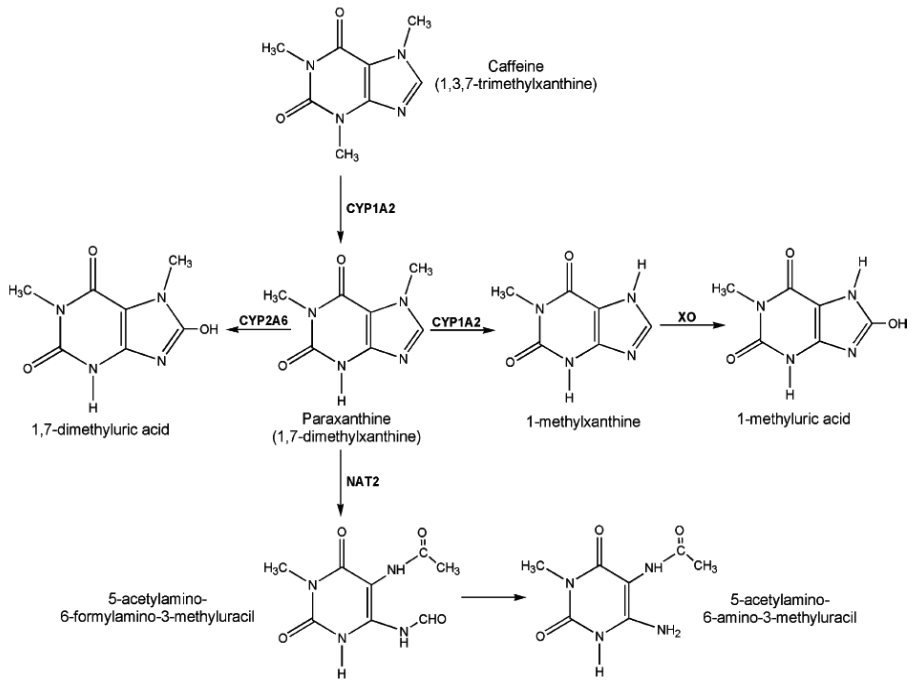


Figure 1 Major liver pathway in caffeine metabolism. Adapted from Krul and Hageman (1998)

Caffeine appears to exert its biological effects through the antagonism of the adenosine receptors (figure 2). Some known physiological effects, which mostly appear early after administration, include the stimulation of the central nervous system, raised blood pressure, metabolic rate elevation, and diuresis. The concentration of the caffeine in various coffee beverages is quite

different, even among a particular population. It has been assumed that a cup of coffee (240 ml) should contain 100 mg of caffeine, however, a recent study in the US revealed that the amount of the caffeine in a cup of brewed coffee (240 ml), prepared at different coffee shops ranged from 70 to 130 mg (McCusker 2003). Therefore, various preparation methods of coffee in different societies may cause a wide range of caffeine concentration.

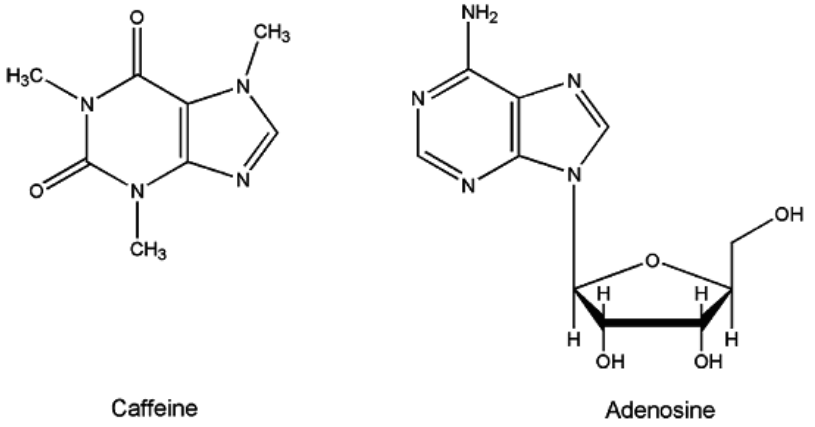


Figure 2 Chemical structures of caffeine and adenosine.

Chlorogenic acid

Green coffee beans contain significant amount of chlorogenic acids, i.e. various isomers of hydroxy-cinnamoyl esters of quinic acid (a common plant constituent). Common to most plants and fruits, green coffee beans can contain as much as 10% of their dry weight of chlorogenic acids. These are mixtures of mono- and di-esters of 3-substituted 4-hydroxycinnamic acid and quinic acid, a sugar-like molecule. Approximately half of the chlorogenic acids lose a molecule of water in the roasting process, thereby forming an internal ester bond that results in a mixture of non-acidic quinolactones (quinides) (Hucke and Maier 1985). Brewing roasted coffee causes the isomerization of the quinides. This results in hundreds of different compounds, each with potentially unique pharmacological actions. Although few of these compounds are present at more than 0.3% of the dry weight of coffee, they still may significantly contributed to the effects of the coffee since these compounds have chemical properties that allow ready entry into the

brain (Olthof et al. 2001). Furthermore, the synergistic effects of different quinides acting on the same biological target may contribute to the health effects of coffee. For coffee drinkers, coffee is the richest dietary source of chlorogenic acids and cinamic acids (caffeic acid). A cup of coffee of 200 ml, contains 70 to 350 mg of chlorogenic acid and 35 to 175 mg of caffeic acid.
Intestine absorbs 95% of caffeic acid and 33% of chlorogenic acid. The remaining chlorogenic acid reaches the colon where it may be hydrolyzed to caffeic acid and quinic acid (Olthof et al. 2003; de Paulis et al. 2002; Olthof et al. 2001; Clifford 1999) (figure 3).

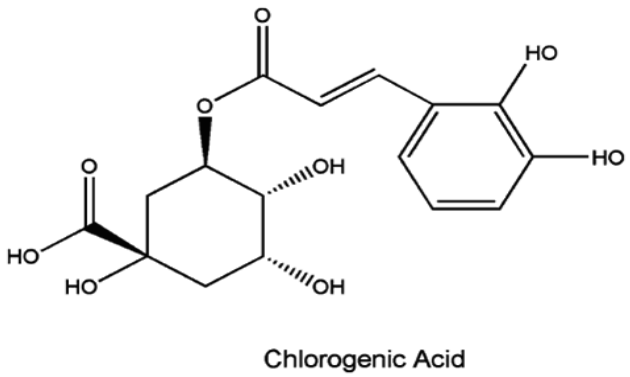


Figure 3 Chemical structure of 5-O-cafeoylquinic acid (chlorogenic acid).

Micronutrients

Some micronutrients found in coffee include magnesium, potassium, vitamin E, and niacin. They may contribute to the observed positive effects of coffee. The amount of the magnesium in a cup of coffee (240 ml) is 1 to 5% of the daily allowance (420 mg/d) and potassium intake is only 1 to 2% (4700 mg/d). Nicotinic acid is a transverse form of trigenolline in coffee beans and a cup of coffee provide 1 to 3 mg per cup and 6 to 18% of daily allowance for niacin (16 mg/d) (U.S. Department of Agriculture and Agricultural Research Service 2004; Institute of Medicine 2004; Institute of Medicine 1997; Institute of Medicine 1998; Adrian and Frangne 1991). Coffee is not a good source of vitamin E since a cup of coffee contains about 0.2 mg of α-tocopherol and 0.2 mg γ-tocopherol, only 0.1% of daily requirement for vitamin E (Institute of Medicine 2000; U.S. Department of Agriculture and Agricultural Research Service 1997).

2.2.2 *Coffee and its impact on Human Health*

Since a great number of people around the world drink coffee, a great concern exists regarding the possible role of coffee on human and public health, since small effects in people could have a large impact on public health. During the last decades, researchers attempted to evaluate health benefits, or harms, received from coffee drinking. Knowledge of both positive and negative health effects of coffee is important to allow individuals to make informed choices regarding coffee consumption. The associations between coffee and caffeine, the fame compound of coffee, with common chronic diseases have been examined through epidemiological, clinical, or experimental research.

Coffee and Parkinson's disease The association between coffee consumption and Parkinson's disease has been evaluated in the wide range of studies. Overall, the results of the case-control studies revealed that coffee and caffeine ingestion are inversely associated with the risk of Parkinson's disease (Hernan et al. 2002). The results from prospective studies are inconsistent. The risk of Parkinson's disease is markedly reduced among men but not women (Ascherio et al 2004; Ascherio et al. 2001; Ross et al. 2000), however, two recent studies from Finland found an inverse association in both men and women (Sääksjärvi et al. 2007; Hu et al. 2007).

Coffee and Cancer Although previous studies, particularly case-control studies, revealed a positive association between coffee and caffeine intake and bladder, ovarian and pancreatic cancers (Zeegers et al. 2001; D'Avanzo et al 1992; Miller et al. 1987), more recent and better designed studies have not confirmed them. Overall recent prospective cohort studies have not observed significant association between coffee consumption or caffeine intake and the risk of the bladder, ovarian, breast, gastric, pancreatic and prostate cancer (Zeegers 2004; Nawrot et al. 2003; Tavani and La Vecchia 2000; Leviton 1990).

2.2.2.1 *Coffee, Glucose Tolerance and Insulin Sensitivity*

Most of the controlled clinical trials have revealed that acute administration of caffeine will impair glucose tolerance and insulin sensitivity (Petrie et al. 2004; Keijzers et al. 2002; Graham et al. 2001; Greer F 2001). Using the hyperinsulinemic-euglycemic glucose clamp method, Keijzers et al. found that caffeine decreased insulin sensitivity by 15% ($P< 0.05$ for trend vs. placebo) in12 healthy volunteers (Keijzers et al. 2002). In another study, 18 young adult men first ingested caffeine (5 mg/kg) or placebo followed one hour later by 75 g of dextrose [oral glucose tolerance test (OGGT)]. Caffeine ingestion resulted in an increase in serum insulin, C peptide and blood glucose for the duration of the OGTT ($P\leq 0.05$ for trend). This suggests that caffeine ingestion may have resulted in insulin resistance (Graham et al. 2001).
Greer et al., investigated glucose disposal following administration of caffeine. Nine healthy, lean, sedentary men underwent two trial sessions one with caffeine (5 mg/kg body wt) and one with placebo (dextrose) administration. Glucose disposal was assessed using the

hyperinsulinemic-euglycemic clamp. Caffeine administration resulted in a significant decrease (24%) in glucose disposal compared to the placebo (Greer et al. 2001).

The effects of coffee consumption over a period of 2 to 4 weeks on serum glucose and insulin level have been examined in a randomized clinical trial. Drinking decaffeinated coffee for 14 days, by prior consumers of an average of 560 mg/d of caffeine from coffee or tea, caused fasting blood glucose level to decrease significantly (Naismith et al. 1970).
Two recent crossover trial studies, examined the effects of coffee and caffeine on fasting blood glucose and insulin levels. In the first study, participants, who were regular coffee consumers of five to eight cups per day, were randomly assigned to drink one liter filtered coffee containing 1100 mg of caffeine for four weeks and then four weeks abstention. They found a higher fasting insulin level, but no effects on the fasting glucose level after coffee period compared to abstention. The second crossover study, which examined participants consuming a weaker caffeine, regular paper filtered coffee, or placebo, found similar fasting glucose concentrations and a nonsignificant association with higher fasting insulin concentrations (van Dam et al. 2004a).

Battram et al. compared the acute effects of caffeine or coffee ingestion on glucose metabolism and found impaired glucose tolerance following both. While caffeine ingestion resulted in higher glucose, insulin, and C peptide responses compared to both placebo and decaffeinated coffee, regular coffee consumption only resulted in an attenuated response for glucose and insulin when compared with decaffeinated coffee, but no difference compared to the placebo (Battram et al. 2006).

Although most of the short term trials of coffee and caffeine ingestion demonstrate the negative impacts on glucose tolerance and insulin sensitivity, epidemiological studies reveal that chronic consumption of coffee may help to maintain normal glucose tolerance.
Cross-sectional studies from diverse countries have found that coffee consumption is inversely associated with the prevalence of impaired glucose tolerance after oral glucose load (Yamaji et al 2004; Soriguer et al. 2004; Agardh et al. 2004).
For instance, Yamaji et al performed a cross-sectional study of 3224 males to investigate the relationship between coffee consumption and glucose tolerance. A total of 1130 men were identified as having glucose intolerance. Fasting and 2-h post-load plasma glucose level were 1.5% and 4.3% lower in those who drank five cups of coffee or more per day compared to those who did not drink coffee. Thus they concluded that coffee may help to prevent postprandial hyperglycemia (Yamaji T et al 2004).
Another cross-sectional study comprised 7949 healthy Swedish subjects aged 35-56. An oral glucose tolerance test identified 107 participants with previously undiagnosed type 2 diabetes and 339 participants with impaired glucose tolerance. The relative risks of type 2 diabetes and impaired glucose tolerance in those drinking five cups of coffee or more per day compared with two cups or less per day in men were 0.45 (95% CI 0.22-0.92) and 0.63 (95% CI, 0.41-0.97) and in women 0.27 (95% CI 0.11-0.66) and 0.47 (95% CI 0.27-0.76). High coffee consumption ($\geq$5 cups/day) was inversely associated with insulin resistance in those subjects with type 2 diabetes and impaired glucose tolerance.
The recently published results of the cohort studies are consistent with these cross-sectional studies. A prospective cohort study of Dutch men and women found an inverse association between habitual coffee consumption and the risk of developing impaired glucose tolerance (OR=0.37, 95% CI 0.16–0.84 for $\geq$7 vs. $\leq$2cups per day). No association between coffee

consumption and impaired fasting glucose emerged (OR=1.35, 95%CI, 0.80–2.27 for ≥7 vs. ≤2 cups per day), which may be interpreted as coffee consumption affects post-load glucose metabolism more than fast glucose (van Dam et al. 2004b). In addition, another prospective study from the U.S. investigated the association between coffee consumption and incident diabetes based on the OGGT and examined coffee habits in those with impaired glucose separately from those with normal glucose. They found that current or past coffee drinkers had a 60% reduced risk of type 2 diabetes compared with those who never drank coffee (past vs. never, OR=0.38, 95% CI, 0.17-0.87, current vs. never OR=0.36, 95% CI, 0.19-0.68). In addition, those who had impaired glucose at the baseline were similarly protected against incident diabetes (past vs. never, OR=0.31 95% CI, 0.11-0.87, current vs. never OR=0.36, 95% CI, 0.16-0.83) (Smith et al. 2006).

2.2.2.2 *Coffee and Type 2 Diabetes*

Although various health effects of coffee have been extensively investigated until recently the association of coffee consumption and development of type 2 diabetes has not been thoroughly studied.
A prospective study of about 17,000 Dutch men and women found that the risk of developing type 2 diabetes was 50% lower in those who drank seven cups of coffee daily compared to those who drank two cups or less (95% CI, 0.35-0.72) (van Dam and Feskens 2002).
Two large prospective cohort studies, the U.S. Health Professional Follow-up Study including 41,934 men and the Nurses' Health Study including more than 84,000 women, revealed that in men who drank at least six cups of coffee daily the risk of developing type 2 diabetes is 54% less than men who abstain from coffee abstainers (95% CI, 0.26-0.82). Among women with the same amount of coffee consumption they observed a 29% lower risk in habitual coffee consumers compared to coffee abstainers (95% CI, 0.56-0.89) (Salazar-Martinez E 2004). A moderate inverse association was also observed between decaffeinated coffee and the risk of type 2 diabetes in those cohorts.

In a study on the Finnish twin cohort, there was a 35% risk reduction (95% CI, 0.44-0.96) among those who drank seven cups of coffee or more compared with those who drank two cups or less (Carlsson 2004).
In another cohort of Swedish women, those who drank three cups of coffee had a 50% lower risk of type 2 diabetes than those who drank two cups or less (95% CI, 0.22-1.06) (Rosengren 2004).
Another community-based cohort from the U.S, which examined the effect of coffee and sweetened beverage consumption on the risk of type 2 diabetes, showed the same inverse association in these community-based U.S. African American and Caucasian adults with a 23% decreased risk (95% CI, 0.61-0.98) in men and 33% (95% CI, 0.45-0.96) in women compared to abstainers (Paynter et al. 2006).
An 11-year prospective study of about 29,000 postmenopausal women found an inverse association between coffee consumption and the risk of type 2 diabetes, particularly in decaffeinated coffee consumers (RR=0.79, 95% CI, 0.50-0.88) (Pereira MA et al. 2006). The Nurses' Health Study II, which included 88,259 U.S. women aged 26-46, evaluated the association between coffee and caffeine and the risk of type 2 diabetes. The relative risk of type 2 diabetes was reported as 0.87 (95% CI, 0.73-1.03) for one cup/day, 0.58 (95% CI, 0.49-0.68)

for 2-3 cups/day, and 0.53 (95% CI 0.41-0.68) for four or more cups of coffee per day compared to non-drinkers (P <0.0001 for trend). This study indicated an inverse association of both caffeinated and decaffeinated coffee with the risk of type 2 diabetes (van Dam et al. 2006).
Also, in a recently published Japanese study, including 17,413 people, the risk of type 2 diabetes for those who drank three or more cups of coffee daily was 42% lower than those who drank 1 cup or less per week (RR=0.58, 95% CI, 0.37-0.90) (Iso et al. 2006). Table 1 summarizes the results of the 14 prospective cohort studies on coffee consumption and the risk of type 2 diabetes.

Not all recent data were observed as an inverse association between the coffee consumption and type 2 diabetes. In fact an earlier Finnish cohort study of more than 19,000 men and women (1973-1977), with an average follow-up of 14 years, found a positive association between coffee consumption and type 2 diabetes (Reunanen et al. 2003). Also, a study of Pima Indians found no association between the coffee consumption and the risk of type 2 diabetes (Saremi et al. 2003).

A systematic review of about nine cohort studies revealed that the risk of developing type 2 diabetes in participants who drank four to six cups or more than six to seven cups of coffee per day to be 28% and 35% lower than those who drank less than two cups daily. They found the same inverse association between coffee consumption and impaired glucose tolerance or type 2 diabetes in cross-sectional studies (van Dam and Hu 2005).

Overall, the results of this brief review of the literature supports the hypothesis that habitual coffee consumption may be associated with a substantially lower risk of type 2 diabetes and glucose intolerance in both men and women.

Table 1. ***Cohort studies of coffee consumption and risk of type 2 diabetes***

Reference Study	Population	Cases	Association	Adjustment	Hazard ratio for highest to lowest category
van Dam & Feskens, 2002	17,111 M*, F* (Netherland)	306	Inverse	Age, sex, educational level, physical activity, alcohol consumption, cigarette smoking, history of CVD, hypertension, hypercholesterolaemia	0.50, ≥7 cups/d, P<0.002
Saremi et al., 2003	2680 M, F (US)	824	Not Significant	Age, sex and BMI	0.92, ≥3 cups/d, P=0.60
Reunanen et al., 2003	19518 M, F (Finland)	855	Not Significant	Age, sex, BMI, smoking, and physical activity	0.92, ≥7 cups/d,
Salazar-Martinez et al., 2004	41,934 M (US)	1333	Inverse	Age, BMI , total caloric intake, family history of diabetes; alcohol consumption, smoking status, physical activity, and dietary factors	0.46, ≥6 cups/d, P=0.007
Salazar-Martinez et al., 2004	84,276 F (US)	4085	Inverse	Age, BMI , total caloric intake, family history of diabetes; alcohol consumption, smoking status, physical activity, menopausal status and postmenopausal hormone use, and dietary factors	0.92, ≥6 cups/d, P<0.001
Tuomilehto et al., 2004	6974 M, 7655 F (Finland)	381	Inverse	Age, sex, BMI, blood pressure, education, physical activity, alcohol and tea consumption, and smoking	Men: 045, ≥10 cups/d, P=0.12 Women: 0.21, ≥10 cups/d, P<0.001
Rosengren et al., 2004	1361 F (Sweden)	74	Inverse	Age, smoking, physical activity, education and BMI	0.57, >6 cups/d, P=0.029
Carlsson et al., 2004	10,652 M, F (Finland)	408	Inverse	Age, sex, BMI, education, physical activity, alcohol consumption, smoking	0.65, ≥7 cups/d
Van Dam et al., 2004	1312 M, F (Netherland)	128	Not Significant	BMI, smoking, physical activity, alcohol consumption and dietary factors	0.92, ≥7 cups/d, P=0.09
Periera et al., 2006	28,812 F (US)	1418	Inverse	Age, education, baseline hypertension, alcohol consumption, smoking, BMI, waist-hip ratio, physical activity, Keys score, tea consumption, soda consumption, and dietary factors	0.78, ≥6 cups/d, P=0.06
Paynter et al., 2006	5414 M, 6,790 F (US)	1437	Inverse	Age, race, smoking, education, alcohol consumption, hypertension, energy intake, BMI, obesity, waist to hip ratio, magnesium	0.77, ≥4 cups/d, P=0.02
Iso et al., 2006	6727 M, 10686 F (Japan)	444	Inverse	Age, sex, BMI, family history of diabetes, smoking, alcohol intake, magnesium, physical activity, and consumption of other beverages	0.58, ≥ 3 cups/d, P=0.027 (total)
Van Dam et al, 2006	88,259 F (US)	1263	Inverse	Age, smoking status, BMI, physical activity, alcohol consumption, use of hormone replacement therapy, oral contraceptive use, family history of type 2 diabetes, hypertension, hypercholesterolemia, consumption of sugar-sweetened soft drinks, consumption of punch, and dietary factors	0.53, ≥4 cups/d, P<0.0001
Bidel et al., 2007	10,666 M, 11,160 F (Finland)	862	Inverse	Age, BMI, alcohol consumption, smoking, and physical activity	Men: 071, ≥7 cups/d, P=0.02, Women: 0.47, ≥7 cups/d, P<0.0001

* M: Male, F: Female

3. AIMS OF THE STUDY

The first aim of this study was to determine the relationship between coffee consumption and the incidence of type 2 diabetes among middle aged Finnish men and women and to examine joint associations of coffee consumption and other factors (including physical activity, obesity and alcohol consumption) with the risk of type 2 diabetes. (Study **I**, **III**)

The second aim of this study was to review the association between coffee drinking and glucose tolerance, the glucose and insulin levels. (Study **II**)

The third aim of this study was to evaluate the relationship between coffee drinking and serum γ-glutamyltransferase on the risk of type 2 diabetes. (Study **IV**)

The fourth aim of this study was to assess the association between coffee consumption and cardiovascular disease mortality among diabetic subjects. (Study **V**)

4. POPULATION AND METHODS

4.1 *Study population*

This study design is based on the FINRISK database. FINRISK is a large population survey on the risk factors of chronic, noncommunicable diseases. The survey is carried out every five years using independent, random and representative population samples of different parts of Finland. Data from the FINRISK surveys are used for many different research projects and for the national health monitoring needs. In addition to CVD and the classical risk factors, the recent research activities also deal e.g. with asthma and allergy, alcohol, socioeconomic factors and genetic epidemiology (Table 2).

Table 2. ***Finrisk Study: Some parameters in the baseline survey among the entire population according to baseline examination years.***

	1972	1977	1982	1987	1992	1997	2002	Total
No.of participants	11870	11408	9343	6235	6051	8259	8847	62013
Sex (men %)*	49.0	48.6	49.4	47.7	47.1	50.0	46.4	48.4
Sex (women %)*	51.0	51.4	50.6	52.3	52.9	50.0	53.6	51.6
Age (years)	41.5	44.3	44.8	45.1	45.2	48.5	48.2	45.1
Age range (years)	25-59	25-64	25-64	25-64	25-64	25-74	25-74	25-74
Follow-up time (years)								
Education (years)	7.8	8.1	9.1	9.9	11.2	11.4	12.3	9.7
Body mass index	25.9	26.1	26.1	26.5	26.3	26.7	26.9	26.3
Waist circumference (cm)	-	-	-	86	87	88	89	88
Waist-to-hip-ratio	-	-	-	0.84	0.85	0.86	0.90	0.87
Systolic blood pressure (mmHg)	146	144	141	140	136	136	137	141
Diastolic blood pressure (mmHg)	91	88	84	84	82	82	79	85
Total cholesterol (nnol/L)	6.6	6.4	6.1	6.0	5.6	5.6	5.6	6.0
HDL-cholesterol (mmol/L)	-	-	1.34	1.44	1.40	1.39	1.50	1.42
Triglycerides (mmol/L)	-	-	-	-	1.53	1.50	1.44	1.49
Serum gamma-glutamyltransferase (GGT) (U/L)	-	-	22.7	22.6	28.1	35.9	34.4	29.0
C-Reactive protein CRP (mg/L)	-	-	-	-	-	2.43	1.74	2.06
Coffee consumption (cups/day)	5.4	5.0	5.2	5.1	4.4	4.3	4.2	4.9
Tea consumption (cups/day)	0.6	0.8	1.0	0.7	0.9	0.9	0.8	0.8
Milk consumption (cups/day)	4.0	3.6	2.9	2.5	2.1	2.1	2.1	2.9
Current smokers (%)*	33.0	29.1	30.0	27.5	29.7	25.3	27.7	29.2
Alcohol drinkers (%)*	46.6	45.0	44.8	47.8	60.8	56.7	65.4	51.6
History of diabetes (%)*	1.3	2.5	2.0	2.5	2.0	3.3	3.3	2.4
Occupational physical activity†	+	+	+	+	+	+	+	+
Commuting physical activity†	+	+	+	+	+	+	+	+
Leisure-time physical activity†	+	+	+	+	+	+	+	+
Dietary habits(FFQ)	-	-	-	-	+	+	+	

Values are given means unless otherwise indicated.

*Values are percentages.

† "+" data are avaiable; "-" data are not avaiable.

Baseline surveys were carried out in two eastern Finnish provinces, North Karelia and Kuopio in 1972 and 1977, and in the Turku-Loimaa region in southwestern Finland in 1982, 1987, 1992 and 1997. The survey was expanded to the Helsinki capital area in 1992 and 1997 and the Oulu province in northern Finland in 1997 (Vartiainen et al., 2000). In each study year, according to the international WHO MONICA (MONItoring trends and determinants in CArdiovascular disease) project protocol (Pajak et al. 1988), the sample was randomly drawn from the population aged 25-64 and was stratified so that in each area at least 250 subjects were chosen from both sexes and each 10-year age group. In 1997, an additional sample of subjects aged 65-74 years was conducted.

The surveys were independent, i.e., the study subjects were chosen from the population randomly for each survey. Participants who belonged to more than one survey were only included in the first survey (Table 2).

Study ethical consideration The study was conducted according to the national data protection legislation, the ethical rules of the Finnish National Public Health Institute, and the rules and principles of the Helsinki Declaration.

Study participants Study **I** was limited to surveys from 1982, 1987, and 1992 and included the participants between the ages 35 to 64. The final sample in study **I** comprised 6,974 men and 7,655 women.

In study **II** a sub-sample (age 45 to 64) comprising 3404 subjects (Tuomilehto et al. 1991) in 1987 and of 2833 subjects in 1992 were invited to receive the standard OGTT at the baseline. Since the fasting time was short in 1987, all the subjects with an abnormal OGTT result at the first screening were invited to attend the second OGTT soon after. In addition, a control group, matched for the 10-year age group and gender, with normal glucose tolerance in the first OGTT was also invited to the second OGTT in 1987. The second OGTT in 1987 was performed after an overnight fast. A total of 803 participants in 1987 and 2153 participants in 1992 attended the OGTT.

Studies **III** and **IV**, also included, in addition to the surveys from 1982, 1987, and 1992, participants from the survey in 1997. In studies **III** and **IV**, the analyses were limited to participants between the ages 35 to 74. These two analyses included a total of 10,188 men and 11,197 women for study **III** and 10,666 men and 11,160 women for study **IV**.

Study **V** included participants from all six surveys from 1972 to 1997. Furthermore, participants' age was expanded from 25 to 74 years. This evaluation included a total of 4,453 patients with a type 2 diabetes diagnosis.

The exclusion criteria The exclusion criteria include subjects with ***known diabetes*** at the baseline (study **I**, **II**, **III**, and **IV**), ***diagnosed with CHD or stroke*** (study **I**, **III**, **IV**, and **V**), ***having type 1 diabetes*** at the baseline or detected during the follow-up period (study **I**-**V**), and subjects ***with missing data*** in all five studies.
The analyses excluded participants younger than 25 (study **V**), 35 (study **I**, **III**, **IV**), and 45 (study **II**), and older than 64 (study **I**, **II**) and 74 (study **III**, **IV**, **V**).

Participation rate The participation rates were varied by the year and sex, but it was not less than 74% and up to 88% in all five studies.

4.2 *Measurements*

4.2.1 *Questionnaire*

Along with the invitation to the survey, a self-administered questionnaire was sent to the participants to be completed at home before arrival to the health care center for anthropometric measurements. Then it was checked by study nurses at the survey sites. The questionnaire included questions on medical history, socioeconomic factors, smoking habits, physical activity, dietary habits, and education level.

Coffee & tea assessment For the assessment of coffee and tea consumption, the participates were asked, "How many cups of coffee or tea do you drink per day (1 cup of coffee equal to 1 deciliter; 1 cup of tea equal to 2 deciliter)?" (Greenland 1993) Coffee consumption was categorized into three to five categories (Study **I**: ≤2, 3-4, 5-6, 7-9, and ≥10 cups/day; Study **III**: 0-2, 3-6, and ≥7 cups/day; Studies **IV**, **V**: 0-2, 3-4, 5-6, and ≥7 cups/day).
The categorization differed between the studies, to ensure enough sample size in each category.
Tea consumption was categorized into three categories in all studies, none, 1-2 cups, and ≥3 cups, because only a few people drank tea.
The type of coffee consumption was assessed in the surveys of 1987 and 1992. More than 80% of the Finnish coffee consumers used filtered coffee at the baseline.

Physical activity included occupational, commuting, and leisure time physical activity. The subjects reported their occupational physical activity according to the following three categories: low, moderate, and high. The daily commuting return journey to work was grouped into three categories: (i) using motorized transportation, or not working outside home (0 min of walking or cycling); (ii) walking or bicycling 1–29 min; (iii) walking or bicycling for more than 30 min. Self-reported leisure time physical activity was classified into three categories: low, moderate, and high; (i) low was defined as subjects who reported low levels of occupational, commuting (<30 min) and leisure time physical activity; (ii) moderate was defined as subjects who reported only one of the three kinds of moderate to high physical activity; (iii) high was defined as subjects who reported two or three kinds of moderate to high physical activity.

Alcohol consumption was assessed with questions on type (beer, wine, liquor, spirit), frequency, and amount of alcohol consumed during the previous week. Based on this information, an alcohol index was calculated indicating the intake of absolute alcohol in grams per week.
In study **IV**, since questions on alcohol consumption were different between the first two surveys (1972 and 1977) and the latter surveys, the participants were categorized into abstainers and alcohol users.

Education level, measured as the total number of school years, was divided into birth cohort specific tertiles.

Smoking Based on the responses, the participants were classified as never, ex-, and current-smokers. Current smokers were categorized into those who smoked less than 20 or 20 or more cigarettes per day.

Dietary assessment The participants' diet and food choices were assessed by two type questions. First, the amount of food consumed daily and second, the frequency of consumption of vegetables and fruits over the last week (<1 time/week, 1-2 times/week, 3-5 times/week, 6-7 times/week), and the frequency of consumption of sausages over the past 12 month (<1 time/month, 1-2 times/month, 1 time/week, 2 times/week, almost daily, >1 time/day) were inquired.

4.2.2. *Anthropometric and laboratory measurements*

At the survey site, specially trained research nurses measured height and weight of the participants who were in light clothing, without shoes by using the standardized WHO MONICA protocol (Pajak et al. 1988). The body mass index (BMI, kg/m^2) was used as a measure of relative body weight as a continuous variable. Blood pressure was measured from the right arm of the participant who was seated for 5 min before the measurement using a standard sphygmomanometer.
After blood pressure measurement, a venous blood specimen was drawn. Total serum cholesterol was determined using the Lieberman-Burchard method in 1972 and 1977, and an enzymatic method (CHOD-PAP, Boehringer MANNHEIM, Mannheim, Germany) since 1982. The enzymatic assay method gave 2.4% lower values than the Lieberman-Burchard method. The cholesterol values from 1972 and 1977 were corrected by this percentage.

In addition, a 2-hour 75g OGTT was carried out by trained nurses in the sub sample of the cohort in study **II**. Furthermore, serum GGT level was determined from fresh venous blood serum samples using a kinetic method (Oy Medix Biochemica AB, Kauniainen, Finland) based on the recommendation of European Committee for Clinical Laboratory Standards (study **V**).
All samples were analyzed in the same central laboratory located at the Finnish National Public Health Institute in Helsinki.

4.3 *Diagnosis of Diabetes*

During the follow-up period, data on the occurrence of new type 2 diabetes cases were obtained from the National Hospital Discharge Register and the Social Insurance Institutions nationwide register of persons receiving drug reimbursement for diabetes medication. To receive the special reimbursement, the diagnosis of diabetes is assigned by the person's own physician, usually a general practitioner, internist, or specialist in occupational medicine. The statements documenting the diagnosis are then reviewed according to current criteria by expert physicians of the Social Insurance Institution. Thus, the register data include the drug treated diabetic, but not those who

are on diet only. Under the Finnish law, all persons with type 1 or type 2 diabetes are eligible for the reimbursement, and thus this registry probably includes virtually all new cases that need medication for type 2 diabetes. Nevertheless, it is well known that the majority of type 2 diabetic patients sooner or later will require pharmacotherapy, and thus, it is likely that the date of ascertainment of diabetes is delayed in our cohort. The National Hospital Discharge Register includes in-hospital admissions of patients to hospitals with a primary or secondary diagnosis of diabetes in Finland nationwide.

4.3.1 *Prospective follow-up*

In study **I**, the follow-up of each participant continued until the diagnosis of type 2 diabetes, the end of 1998, or until death. In study **III**, the follow-up of each cohort member continued until the date of the diagnosis of type 2 diabetes, death, or until the end of 2003. In study **IV**, follow-up time was calculated from the baseline examination to the date of diagnosis of type 2 diabetes, death or the end of 2002.
In study **V**, study cohorts were followed until death or the end of 2003 through computerized register linkage. Mortality data were obtained from Statistics Finland and were linked with the survey data using the personal identification number assigned for every resident in Finland. The Eighth, Ninth and Tenth Revisions of the International Classification of Diseases were used to identify diabetic cases (250, 250.0 250.2, and E11) and deaths from CHD (410-414 and I20-I25), stroke (430-438 and I60-I66), and CVD (390-459 and I00-I99).

4.4 *Statistical analyses*

4.4.1 *Prospective studies (study I, III, IV, V)*

Sex-specific differences in risk factors based on different levels of coffee consumption were tested using either the univariate analysis of variance (ANOVA) or logistic regression after adjustment for age and study year. The Cox proportional hazard models were used to estimate the single and joint effects of coffee consumption, and physical activity, BMI, and alcohol consumption on the risk of type 2 diabetes. Tests for trends were conducted using median values for each category of coffee consumption (studies **I, III, IV**). The proportional hazard assumption in the Cox models was assessed with graphical methods and with models including time-by-covariate interactions (Cox 1972) (studies **I**, **III**, **V**). In general, all proportionality assumptions were appropriate.
The assumption of Cox proportional hazard model was tested using Schoenfeld residuals by the Stata statistical [package] (STATA press 2001) and found not to be violated (study **IV**).
In study **IV,** analyses were stratified by the serum GGT levels classified into two classes using the 75^{th} sex specific percentiles as the cut-points (40 U/L in men, 21 U/L in women).
In study **V,** the associations between coffee consumption at the baseline and the risk of total, CVD, CHD, and stroke mortality were analyzed by using Cox proportional hazards models. Different levels of coffee consumption were included in the models as dummy variables and the significance of the trend over different categories of coffee consumption was tested in the same models by giving an ordinal numeric value for each dummy variable.

4.4.2 *Cross-Sectional study (study II)*

Linear regression models were applied to test the association between coffee consumption and glucose and insulin levels (study **II**). Logistic regression was applied to the association between coffee consumption and hyperglycaemia and hyperinsulinemia (study **II**). All analyses were adjusted for age, study year, BMI, systolic blood pressure, education, alcohol and tea drinking, smoking and occupational, commuting and leisure time physical activity.
First level of interactions between coffee consumption and sex were analyzed to assess whether the effect differed between the sexes. Because no statistically significant interactions were found, men and women were combined in the analyses adjusted for sex. The possibility of a non-linear association between coffee consumption and glucose and insulin levels (hyperglycaemia and hyperinsulinemia) was tested by a likelihood ratio test comparing regression models without and with the squared term for the relevant coffee consumption variable. No significant quadratic or higher order effects on the association between coffee consumption and glucose and insulin levels were observed.

All statistical analyses in studies **I**, **II**, **III** and **V** were performed with SPSS for Windows 11.0-13.0 (2002-2005) (SPSS Inc, Chicago, Ill). In study **IV** analyses were carried out by the PHREG procedure of the SAS statistical package (version 8.02) (SAS institute 2003).

5. RESULTS

5.1 *Coffee consumption and the incidence of type 2 diabetes*

In studies **I**, **II**, and **IV** we analyzed the association between coffee consumption and risk of type 2 diabetes.

In study **I** (Table 3), during the 12 years of follow-up period time 381 individuals with type 2 diabetes were found. Age- and study year-adjusted hazards ratios (HRs) of diabetes in people who drank 0-2, 3-4, 5-6, 7-9, and ≥10 cups of coffee were 1.00, 0.72, 0.49 0.47, and 0.26 (P=0.002 for trend) in women, and 1.00, 0.83, 0.88, 0.86, and 0.69 (P=0.74 for trend) in men.

After further adjustments for other covariates (BMI, systolic blood pressure, education, occupational, commuting and leisure time physical activity, alcohol and tea consumption, and smoking), this inverse association still remained significant among women (P<0.001 for trend). In men, a similar trend was observed and the risk of diabetes was significantly reduced in those who drunk at least 10 cups of coffee (HRs, 0.45 95% CI, 0.25-0.81). When men and women were combined, sex- and multivariate-adjusted HRs by the coffee consumption of 0-2, 3-4, 5-6, 7-9, and ≥10 cups were 1.00, 0.76, 0.54, 0.55, and 0.39 (P<0.001 for trend). The risk of diabetes did not differ between total coffee abstainers and light coffee drinkers (HRs, 1.20 95% CI, 0.74-1.97). Sex- and multivariate-adjusted (including coffee consumption) HRs of diabetes by the tea consumption of 0, 1-2, and ≥3 cups were 1.00, 0.81, and 0.98 (P=0.27 for trend) (Table 4).

Table 3. ***Baseline characteristics of participants by volume of coffee consumption* in study I***

	Daily coffee consumption					*P* value for trend
	≤2 cups	3-4 cups	5-6 cups	7-9 cups	≥10 cups	
Men						
No. of subjects	1251	1732	2185	943	863	
Age, mean (SD), y	49.1 (8.4)	49.0 (8.5)	48.8 (8.4)	47.7 (8.1)	46.3 (7.9)	<0.001
Body mass index, mean (SD)	26.6 (3.7)	27.0 (3.6)	27.1 (3.7)	27.0 (3.7)	27.3 (4.1)	<0.001
Systolic blood pressure, mean (SD), mm Hg	143 (19)	143 (19)	144 (19)	144 (18)	143 (23)	0.101
Diastolic blood pressure, mean (SD), mm Hg	89 (12)	88 (11)	88 (11)	87 (12)	86 (12)	<0.001
Education, mean (SD), y	9.9 (4.2)	9.5 (3.8)	8.9 (3.6)	8.5 (3.2)	8.4 (3.3)	<0.001
Low occupational physical activity, No. (%)	573 (46)	737 (43)	852 (39)	307 (33)	279 (32)	<0.001
Low leisure time physical activity, No. (%)	342 (27)	455 (26)	627 (29)	313 (33)	311 (36)	<0.001
Walking or cycling to/from work <30 minutes, No. (%)	1056 (84)	1472 (85)	1901 (87)	804 (85)	735 (85)	0.211
Tea drinker, No. (%)	847 (68)	766 (44)	539 (25)	124 (13)	91 (11)	<0.001
Alcohol drinker, No. (%)	757 (61)	1065 (61)	1283 (59)	533 (57)	482 (56)	0.004
Current smoker, No. (%)	211 (17)	379 (22)	655 (30)	370 (39)	481 (56)	<0.001
Obesity, No. (%)†	214 (17)	324 (19)	431 (20)	171 (18)	189 (22)	0.008
Women						
No. of subjects	1386	2544	2527	819	379	
Age, mean (SD), y	49.3 (8.8)	49.7 (8.5)	49.0 (8.4)	47.1 (8.0)	45.6 (7.6)	<0.001
Body mass index, mean (SD)	26.4 (4.9)	26.4 (4.7)	26.9 (4.8)	27.3 (4.9)	27.5 (5.0)	<0.001
Systolic blood pressure, mean (SD), mm Hg	141 (22)	141 (22)	141 (21)	139 (20)	138 (20)	0.015
Diastolic blood pressure, mean (SD), mm Hg	84 (11)	84 (11)	84 (11)	82 (11)	82 (11)	<0.001
Education, mean (SD), y	10.0 (4.0)	9.6 (3.7)	9.1 (3.4)	8.8 (3.2)	8.6 (3.5)	<0.001
Low occupational physical activity, No. (%)	726 (52)	1178 (46)	1036 (41)	300 (37)	128 (34)	<0.001
Low leisure time physical activity, No. (%)	466 (34)	763 (30)	912 (36)	333 (41)	164 (43)	<0.001
Walking or cycling to/from work <30 minutes, No. (%)	1085 (78)	1890 (74)	1923 (76)	618 (76)	292 (77)	0.037
Tea drinker, No. (%)	920 (66)	1113 (44)	645 (26)	122 (15)	48 (13)	<0.001
Alcohol drinker, No. (%)	572 (41)	1051 (41)	905 (36)	302 (37)	145 (38)	0.003
Current smoker, No. (%)	93 (7)	229 (9)	346 (14)	148 (18)	147 (39)	<0.001
Obesity, No. (%)	278 (20)	512 (20)	577 (23)	192 (23)	82 (22)	<0.001

*Adjusted for age and study year.

†Obesity was defined as body mass index ≥ 30.

Table 4. ***Hazard ratios for the development of type 2 diabetes by volume of coffee consumption (study I).***

	Daily coffee consumption					***P* value for trend**
	≤2 cups	**3-4 cups**	**5-6 cups**	**7-9 cups**	**≥10 cups**	
Men						
No. of new cases	41	48	67	28	19	
Person-years	14191	20054	25704	11480	10426	
Adjustment for age and study year	1.00	0.83 (0.54-1.25)	0.88 (0.60-1.30)	0.86 (0.53-1.39)	0.69 (0.40-1.19)	0.735
Further adjustment for other factors*	1.00	0.73 (0.47-1.13)	0.70 (0.45-1.05)	0.67 (0.40-1.12)	0.45 (0.25-0.81)	0.116
Women						
No. of new cases	46	68	48	13	3	
Person-years	15821	30367	32036	10523	4980	
Adjustment for age and study year	1.00	0.72 (0.49-1.04)	0.49 (0.32-0.73)	0.47 (0.25-0.87)	0.26 (0.08-0.85)	0.002
Multivariate adjustment*	1.00	0.71 (0.48-1.05)	0.39 (0.25-0.60)	0.39 (0.20-0.74)	0.21 (0.06-0.69)	<0.001
Men and women combined†						
No. of new cases	87	116	115	41	22	
Person-years	30112	50421	57740	22003	15406	
Adjustment for age and study year	1.00	0.79 (0.59-1.04)	0.67 (0.50-0.88)	0.66 (0.46-0.96)	0.53 (0.33-0.85)	0.016
Multivariate adjustment	1.00	0.76 (0.57-1.01)	0.54 (0.40-0.73)	0.55 (0.37-0.81)	0.39 (0.24-0.64)	<0.001

*Adjusted for age, study year, body mass index, systolic blood pressure, education, occupational physical activity (light, moderate, and active), walking or cycling to/from work (0, 1-29, and ≥30 minutes per day), leisure time physical activity (low, moderate, and high), cigarette smoking (never, past, and current smoking of 1-19 or ≥20 cigarettes per day), alcohol consumption (0, 1-100, 101-300, and >300 g per week), and tea consumption (none, 1-2, and ≥3 cups per day).

†Also adjusted for sex.

5.1.1 *Joint association of coffee consumption and other factors on the risk of type 2 diabetes*

In study **III** (Table 5, 6), 964 cases of type 2 diabetes were identified during a mean follow-up period of 13.4 years. Multivariate-adjusted (age, study year, systolic blood pressure, education, smoking, physical activity, body mass index, and fruit, vegetable, sausage, bread, alcohol, and tea consumption) HRs of type 2 diabetes in participants who drank 0-2, 3-6 and $\geq$7 cups of coffee were 1.00, 0.77, and 0.66 in men, and 1.00, 0.71, and 0.52 in women. When both sexes were combined, sex- and multivariate-adjusted HRs were 1.00, 0.75, and 0.61 (Table 7).

When coffee consumption was examined as a continuous variable, multivariate-adjusted HRs of type 2 diabetes associated with an increment of one cup of coffee per day were 0.97 in men, 0.91 in women, and 0.95 in both sexes combined.

In multivariate analyses we estimated the joint effects of coffee consumption and any one of the physical activity (Figure 4a), BMI (Figure 4b), and alcohol consumption (Figure 4c) on the risk of type 2 diabetes. Multivariate-adjusted HRs of type 2 diabetes decreased significantly with increasing physical activity. The HRs of type 2 diabetes associated with low, moderate, and high physical activity were 1.00, 0.62, and 0.50 in men, and 1.00, 0.80, and 0.65 (P=0.009 for the trend) in women.

Table 5. ***Baseline characteristics of study sample by sex (study III).***

Variable	Men	Women	*P* value for trend
Number of participants	10188	11197	
Age (y)	50	50	0.80
BMI (kg/m^2)	27	27	<0.001
Diastolic blood pressure (mmHg)	87	83	<0.001
Systolic blood pressure (mmHg)	142	139	<0.001
Education level (y)	10	10	<0.001
Bread consumption (slices/day)	6	5	<0.001
Coffee consumption (%)			
0-2 cups/day	19	20	<0.001
3-6 cups/day	56	65	
≥7 cups/day	24	14	
Physical activity (%)			
Low	11	13	<0.001
Moderate	43	41	
High	46	46	
BMI (%)			
<25 kg/m^2	31	42	<0.001
25-29.9 kg/m^2	50	37	
≥30 kg/m^2	19	21	
Smoking (%)			
Never	36	73	<0.001
Past	29	10	
Current	35	17	
Tea consumption (%)			
None	64	61	<0.001
1-2 cups/day	25	31	
3 cups/day	10	8	
Alcohol consumption (%)			
None	38	60	<0.001
1-100 g/week	38	35	
>100 g/week	25	5	
Daily consumption of vegetables (%)	17	30	<0.001
Daily consumption of fruits (%)	21	40	<0.001
Almost daily consumption of sausage (%)	17	23	<0.001

Values are as means or percentages.

Table 6. ***Baseline characteristics according to different levels of coffee consumption by sex (study III).***

	Coffee consumption (men)			***P* value for trend**	**Coffee consumption (women)**			***P* value for trend**
	0-2 cups/day	**3-6** cups/ day	**≥7** cups/day		**0-2** cups/day	**3-6** cups/day	**≥7** cups/day	
Number of participants	1986	5704	2498		2257	7314	1626	
Age (y)	51	50	48	<0.001	51	50	47	<0.001
BMI (kg/m^2)	27	27	27	0.08	26	27	27	0.22
Diastolic blood pressure (mmHg)	88	87	86	<0.001	83	83	81	<0.001
Systolic blood pressure (mmHg)	143	143	141	<0.001	139	139	135	<0.001
Education level (y)	10	10	9	<0.001	11	10	10	<0.001
Bread consumption (slices/day)	6	6.0	7.0	<0.001	4.5	4.8	5	<0.001
Physical activity (%)								
Low	11	11	10	<0.001	16	12	14	<0.001
Moderate	47	43	41		43	40	37	
High	42	46	49		41	47	49	
BMI (%)								
<25 kg/m^2	33	30	31	0.22	44	42	41	0.27
25-29.9 kg/m^2	49	51	49		35	37	37	
≥30 kg/m^2	18	19	19		20	21	22	
Smoking (%)								
Never	50	37	24	<0.001	78	74	58	<0.001
Past	30	32	24		12	10	11	
Current	20	32	53		10	16	31	
Tea consumption (%)								
None	32	66	87	<0.001	34	65	84	<0.001
1-2 cups/day	39	27	10		44	30	14	
3 cups/day	28	7	3		22	4	1	
Alcohol consumption (%)								
None	36	36	42	<0.001	57	60	63	0.002
1-100 g/week	38	39	35		37	36	32	
>100 g/week	26	25	23		5	4	4	
Daily consumption of vegetables (%)	22	18	12	<0.001	35	29	23	<0.001
Daily consumption of fruits (%)	26	21	16	<0.001	42	41	34	<0.001
Almost daily consumption of sausage (%)	17	16	19	0.017	21	23	22	0.10

Values are as means or percentages.

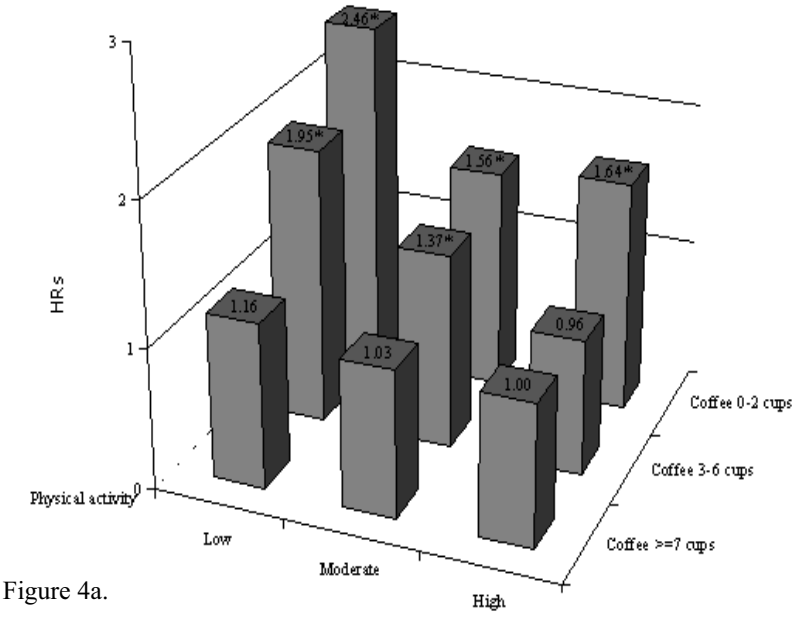


Figure 4a.

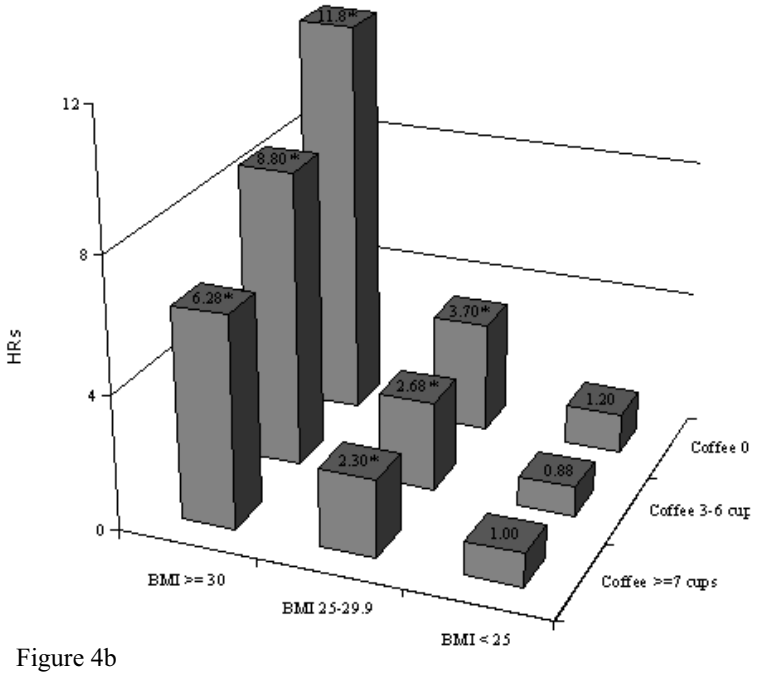


Figure 4b

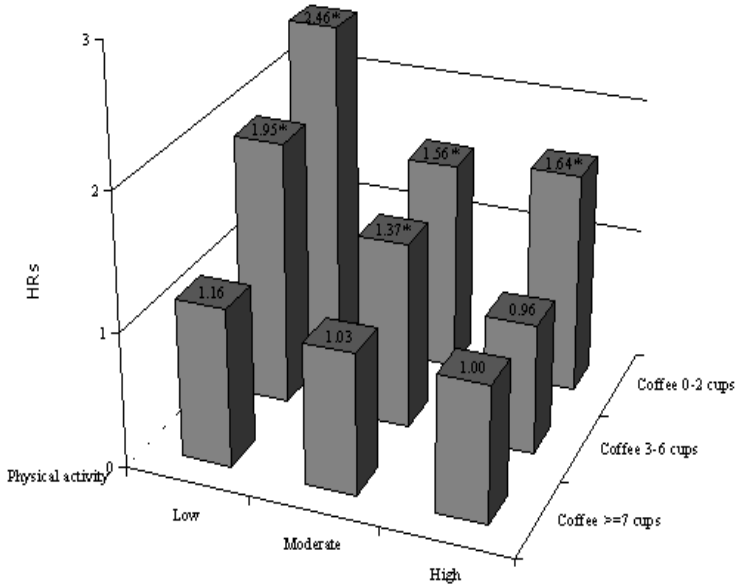


Figure 4. Hazard ratios of type 2 diabetes with joint effects of coffee consumption and physical activity (**a**), coffee consumption and BMI (**b**), coffee and alcohol consumption (**c**). Cox proportional hazards model adjusted for age, study year, sex, education, systolic blood pressure, bread consumption, frequency of vegetable consumption, frequency of fruit consumption, frequency of sausage consumption, tea consumption, and smoking (also for BMI and alcohol consumption in a, physical activity and alcohol consumption in b, physical activity and BMI in c). **P* <0.05 compared with referent group.

Multivariate-adjusted HRs of type 2 diabetes at different levels of BMI were 1.00, 2.90, and 8.46 in men, and 1.00, 2.78, and 9.59 in women.
Multivariate-adjusted HRs of type 2 diabetes in participants who drank 0, 1-100, and >100 g of alcohol per week were 1.00, 0.91, and 0.74 in men, and 1.00, 0.74, and 0.23 in women. When

both sexes were combined, the same results were observed. No significant association between tea consumption and the risk of type 2 diabetes was found (Table 7).

An inverse association between coffee consumption and the risk of type 2 diabetes was found in subjects at different levels of physical activity, at different levels of BMI, and in alcohol drinkers and non-drinkers.The joint association of coffee consumption, physical activity, and BMI with the risk of type 2 diabetes is shown in Figure 5. After adjustment for all confounding factors, coffee consumption was inversely associated with type 2 diabetes incidences at any level of physical activity and BMI; the direct association of BMI and the observed effect of physical activity on the risk of type 2 diabetes was also found at different levels of coffee consumption. The risk of development of type 2 diabetes was about 11 times higher in obese subjects reporting low levels of physical activity and drinking less than two cups of coffee compared to non-obese persons reporting moderate or high level of physical activity and drinking at least seven cups of coffee daily. Among the obese and inactive people, coffee drinking (≥7 versus 0-2 cups per day) reduced the risk of type 2 diabetes to approximately half.

Table 7. ***Hazard ratios for the development of type 2 diabetes by different levels of coffee consumption, physical activity, BMI, tea and alcohol consumption (study III).***

	Number of new cases		**Person-year**		**Adjusted hazard ratio** (95% CI)[a]		
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men and women combined**[b]
Coffee consumption							
0-2 cups/day	103	102	24 089	28 514	1.00	1.00	1.00
3-6 cups/day	289	293	74 314	101 708	0.77 (0.61-0.98)	0.71 (0.56-0.91)	0.75 (0.63-0.89)
≥7 cups/day	125	52	34 233	24 340	0.66 (0.49-0.89)	0.52 (0.36-0.74)	0.61 (0.49-0.76)
P-value for trend					0.022	0.001	<0.001
Physical activity							
Low	100	121	12 644	19 906	1.00	1.00	1.00
Moderate	230	193	54 840	60 655	0.62 (0.48-0.78)	0.80 (0.64-1.01)	0.71 (0.60-0.84)
High	187	133	65 152	74 001	0.50 (0.39-0.65)	0.65 (0.50-0.86)	0.58 (0.48-0.70)
P-value for trend					<0.001	0.009	<0.001
BMI categories							
<25 kg/m^2	44	42	42 084	66 672	1.00	1.00	1.00
25-29.9 kg/m^2	222	126	67 260	57 386	2.90 (2.10-4.02)	2.78 (1.95-3.96)	2.91 (2.29-3.69)
≥30 kg/m^2	251	279	22 292	30 504	8.46 (6.10-11.7)	9.59 (6.83-13.4)	9.17 (7.25-11.6)
P-value for trend					<0.001	<0.001	<0.001
Tea consumption							
None	360	296	86 578	96 794	1.00	1.00	1.00
1-2 cups/day	113	122	32 418	46 375	0.89 (0.71-1.11)	0.92 (0.74-1.15)	0.90 (0.77-1.06)
≥3 cups/day	44	29	13 640	11 393	0.83 (0.59-1.17)	0.85 (0.57-1.27)	0.83 (0.64-1.08)
P-value for trend					0.41	0.61	0.23
Alcohol consumption							
None	223	357	51 068	97 535	1.00	1.00	1.00
1-100 g/week	190	87	50 638	51 204	0.91 (0.75-1.11)	0.74 (0.57-0.94)	0.84 (0.72-0.97)
>100 g/week	104	3	30 930	5823	0.74 (0.58-0.95)	0.23 (0.07-0.73)	0.69 (0.55-0.87)
P-value for trend					0.064	0.004	0.002

[a]Cox proportional hazards model included age, study year, education, systolic blood pressure, bread consumption, frequency of vegetable consumption, frequency of fruit consumption, frequency of sausage consumption, coffee consumption, tea consumption, alcohol consumption, smoking, physical activity, and BMI (as a continuous variable, except BMI as a categorizing variable).
[b]Adjusted also for sex

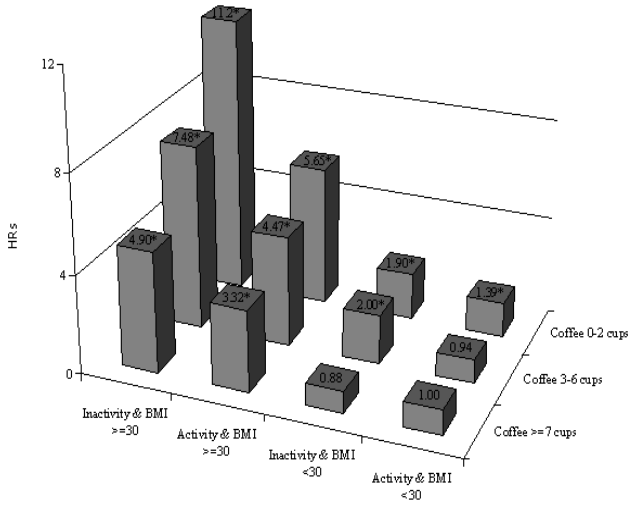


Figure 5. Hazard ratios of type 2 diabetes with joint effects of coffee consumption, physical activity, and BMI. Cox proportional hazards model adjusted for age, study year, sex, education, systolic blood pressure, bread consumption, frequency of vegetable consumption, frequency of fruit consumption, frequency of sausage consumption, tea and alcohol consumption, and smoking. Inactivity was defined as low physical activity; activity was defined as moderate or high physical activity.

*P <0.05 compared with referent group.

5.1.2 *Coffee, serum GGT level and type 2 diabetes*

In study **IV** (Table 8) the same significant inverse association occurred between the coffee consumption and risk of type 2 diabetes among both men and women. Additional adjustment for GGT as a potential confounder did not change the association. Sex- and multivariate-adjusted (age, BMI, alcohol consumption, smoking, and physical activity) HRs of incident type 2 diabetes by coffee consumption decreased linearly with increasing amounts of coffee, being 0.64 for people drinking seven cups or more per day compared to those drinking 0-2 cups of coffee (Table 9).

Table 8. ***Baseline characteristics of participants by volume of coffee consumption (study IV).***

	Daily coffee consumption, cups			
	0-2	**3-4**	**5-6**	**≥7**
Men				
No. of subjects, (%)	1994 (19)	2811 (26)	3275 (31)	2586 (24)
Age, mean (SD), y	52	52	50	48
GGT (U/L, mean)	46	39	33	31
Body mass index, mean (SD)	27	27	27	27
Alcohol consumption, No, (%)				
0 g	18	24	31	27
1-69 g	19	28	32	21
70-139 g	18	27	30	25
140-209 g	19	28	31	21
> 210 g	24	29	24	23
Physical activity at least twice per week (%)	21	28	30	21
Current smoking, No. (%)	14	20	29	47
Women				
No. of subjects, (%)	2205 (20)	3849 (34)	3481 (31)	1625 (15)
Age, mean (SD), y	51	51	50	47
GGT (U/L, mean)	26	20	18	17
Body mass index, mean (SD)	26	27	27	27
Alcohol consumption, No, (%)				
0 g	19	33	32	15
1-34 g	21	36	28	15
35-69 g	20	36	28	15
> 70 g	12	10	9	9
Physical activity at least twice per week (%)	48	50	45	40
Current smoking, No. (%)	10	25	35	30

Table 9. ***Coffee consumption and incident diabetes (study IV).***

		Coffee intake (frequency/day)				***P* value for**
		0-2	**3-4**	**5-6**	**≥7**	**trend**
Men						
	No of cases/pop.	87/1994	117/2811	164/3274	115/2586	
	Person-years	22105	32919	40353	33190	
	Incidence rate/1000 Person-years	3.94	3.55	4.06	3.46	
	Age-adjusted RR	1.00	0.89 (0.67-1.17)	1.01 (0.78-1.13)	0.91 (0.69-1.21)	0.86
	Multivariate* RR	1.00	0.89 (0.68-1.18)	0.87 (0.67-1.13)	0.71 (0.53-0.94)	0.02
	Multivariate** RR	1.00	0.93 (0.7-1.22)	0.91 (0.69-1.18)	0.74 (0.55-0.99)	0.05
Women						
	No of cases/pop.	83/2206	131/3849	122/3481	43/1625	
	Person-years	25860	48028	47612	23022	
	Incidence rate/1000 Person-years	3.21	2.73	2.56	1.87	
	Age-adjusted RR	1.00	0.80 (0.61-1.05)	0.76 (0.57-1.0)	0.64 (0.44-0.92)	0.02
	Multivariate* RR	1.00	0.75 (0.57-0.98)	0.63 (0.47-0.83)	0.47 (0.33-0.69)	<0.0001
	Multivariate** RR	1.00	0.78 (0.59-1.03)	0.66 (0.49-0.87)	0.50 (0.34-0.72)	<0.0001
Men and women* **						
	No of cases/pop.	170/4200	248/6660	286/6756	158/4211	
	Person-years	47966	80947	87965	56212	
	Incidence rate/1000 Person-years	3.54	3.06	3.25	2.81	
	Age-adjusted RR	1.00	0.85 (0.70-1.04)	0.89 (0.73-1.07)	0.80 (0.64-0.99)	0.10
	Multivariate* RR	1.00	0.83 (0.68-1.0)	0.75 (0.62-0.91)	0.61 (0.49-0.76)	<0.0001
	Multivariate** RR	1.00	0.85 (0.70-1.04)	0.78 (0.65-0.95)	0.64 (0.51-0.80)	<0.0001

* Adjusted for age, BMI, alcohol consumption, smoking, and physical activity

** Additional adjustment for GGT

***All analyses additionally adjusted for sex

The association between coffee consumption and incident type 2 diabetes was stratified by the baseline GGT level (≤75th, ≥75th percentiles). No association existed between coffee consumption and the incidence of type 2 diabetes among men with low GGT levels, but at a high GGT level an inverse tendency appeared, however, *P*-value for the trend failed to reach the level of significance. Among women with a low GGT level a non-significant inverse trend between coffee consumption and incident diabetes was detected. At a high GGT level a strong inverse association occurred and multivariate-adjusted HRs of diabetes in women who drank 0-2, 3-4, 5-6, and ≥7 cups of coffee were 1.00, 0.75, 0.59, and 0.44. When data for men and women were combined, in the highest quartile of the GGT level sex-, and multivariate-adjusted HRs for type 2 diabetes were 1.00, 0.77, 0.70, 0.65, but no association between coffee and risk for type 2 diabetes was found in pooled data at lower levels of GGT (≤75th percentile). The interaction between coffee, GGT, and sex on the risk of type 2 diabetes has been measured. A significant interaction effect of GGT and coffee consumption on the risk of type 2 diabetes appeared in the data of women (*P*=0.05 for interaction) and in both sexes combined (*P*=0.02 for interaction) (Table 10).

Table 10. ***Coffee consumption and incident diabetes stratified by baseline GGT level (study IV).***

	Coffee intake (frequency/day)				***P* value for trend**
	0-2	**3-4**	**5-6**	**>=7**	
Men		(*P* of interaction=0.18)			
GGT<75th percentile (40U/L)					
No of cases	38/1335	64/2032	110/2519	73/2049	
Person-years	16019	24992	32838	27181	
Incidence rate/1000 Person-years	2.37	2.56	3.35	2.68	
Age-adjusted RR	1.00	1.06 (0.71-1.58)	1.36 (0.94-1.97)	1.18 (0.80-1.75)	0.22
Multivariate* RR	1.00	1.06 (0.71-1.59)	1.14 (0.79-1.66)	0.94 (0.63-1.40)	0.75
GGT>=75th percentile (40U/L)					
No of cases	49/659	53/779	54/756	42/537	
Person-years	6087	7927	7515	6009	
Incidence rate/1000 Person-years	8.05	6.69	7.18	6.99	
Age-adjusted RR	1.00	0.82 (0.56-1.21)	0.93 (0.63-1.37)	0.92 (0.61-1.41)	0.89
Multivariate* RR	1.00	0.85 (0.58-1.26)	0.81 (0.55-1.20)	0.68 (0.44-1.05)	0.08
Women		(*P* of interaction=0.05)			
GGT<75th percentile (21U/L)					
No of cases	33/1452	59/2710	76/2710	30/1322	
Person-years	18390	36692	39428	19615	
Incidence rate/1000 Person-years	1.79	1.61	1.93	1.53	
Age-adjusted RR	1.00	0.82 (0.53-1.25)	0.95 (0.63-1.43)	0.85 (0.52-1.40)	0.85
Multivariate* RR	1.00	0.84 (0.55-1.30)	0.86 (0.57-1.30)	0.68 (0.41-1.13)	0.20
GGT>=75th percentile (21U/L)					
No of cases	50/754	72/1139	46/771	13/303	
Person-years	7471	11336	8184	3407	
Incidence rate/1000 Person-years	6.69	6.35	5.62	3.82	
Age-adjusted RR	1.00	0.92 (0.64-1.31)	0.85 (0.57-1.27)	0.67 (0.36-1.24)	0.19
Multivariate* RR	1.00	0.75 (0.52-1.09)	0.59 (0.39-0.88)	0.44 (0.24-0.82)	0.002
Men and women**		(*P* of interaction=0.02)			
GGT<75th percentile					
No of cases	71/2787	123/4742	186/5229	103/3371	
Person-years	34409	61684	72266	46796	
Incidence rate/1000 Person-years	2.06	1.99	2.57	2.20	
Age-adjusted RR	1.00	0.95 (0.71-1.27)	1.17 (0.89-1.54)	1.04 (0.77-1.41)	0.38
Multivariate* RR	1.00	0.96 (0.71-1.28)	1.01 (0.76-1.33)	0.82 (0.60-1.12)	0.95
GGT>=75th percentile					
No of cases	99/1413	125/1918	100/1527	55/840	
Person-years	13557	19263	15699	9417	
Incidence rate/1000 Person-years	7.30	6.49	6.37	5.84	
Age-adjusted RR	1.00	0.88 (0.68-1.14)	0.89 (0.68-1.18)	0.85 (0.61-1.19	0.51
Multivariate* RR	1.00	0.77 (0.59-1.01)	0.70 (0.53-0.93)	0.65 (0.46-0.91)	0.001

* Adjusted for age, BMI, alcohol consumption, smoking, and physical activity
**All analyses additionally adjusted for sex

5.1.3 *Coffee consumption and risk of type 2 diabetes in subgroup analyses*

Multivariate-adjusted inverse association between coffee consumption and diabetes risk was present in subjects aged 35-49 (P=0.23 for trend) and 50-64 years (P=0.001 for trend). Similarly, the inverse association was observed in non-smokers (P=0.001 for trend), in non-alcohol drinkers (P<0.001 for trend) and in overweight participants (P=0.01 for trend). A nonsignificant association was observed in smokers (P=0.07 for trend), in healthy weight participants (P=0.35 for trend), in participants who were obese (P=0.05 for trend), in alcohol drinkers (P=0.25 for trend), in filtered coffee drinkers (P=0.07 for trend), and in pot-boiled coffee drinkers (P=0.06 for trend). (study **I**) (Table 11).

Table 11. ***Hazard ratios for the development of type 2 diabetes by volume of coffee consumption among various subpopulations* (study I).***

	Daily coffee consumption					*P* value for
	≤2 cups	**3-4 cups**	**5-6 cups**	**7-9 cups**	**≥10 cups**	**trend**
Age <50 years	1.00	0.65 (0.37-1.13)	0.63 (0.37-1.11)	0.57 (0.29-1.15)	0.42 (0.20-0.91)	0.234
Age ≥50 years	1.00	0.82 (0.59-1.16)	0.53 (0.37-0.76)	0.57 (0.35-0.92)	0.38 (0.20-0.74)	0.001
Smoking						
Never	1.00	0.77 (0.53-1.12)	0.44 (0.29-0.66)	0.41 (0.22-0.76)	0.42 (0.18-1.00)	0.001
Ever or current	1.00	0.71 (0.45-1.13)	0.69 (0.44-1.09)	0.71 (0.41-1.22)	0.39 (0.21-0.73)	0.070
Body mass index, kg/m^2						
<25	1.00	0.53 (0.19-1.45)	0.65 (0.25-1.66)	0.36 (0.09-1.48)	0.15 (0.02-1.29)	0.348
25-29.9	1.00	0.74 (0.46-1.18)	0.48 (0.29-0.80)	0.53 (0.28-1.01)	0.26 (0.10-0.68)	0.013
≥30	1.00	0.86 (0.58-1.28)	0.59 (0.39-0.88)	0.59 (0.35-1.01)	0.56 (0.31-1.02)	0.048
Alcohol						
None	1.00	0.79 (0.55-1.13)	0.46 (0.32-0.68)	0.40 (0.23-0.70)	0.45 (0.25-0.83)	<0.001
Drinker	1.00	0.79 (0.47-1.32)	0.78 (0.47-1.32)	0.97 (0.53-1.78)	0.38 (0.16-0.93)	0.247
Type of coffee†						
Filtered coffee	1.00	0.63 (0.34-1.16)	0.51 (0.27-0.96)	0.47 (0.19-1.17)	0.15 (0.03-0.66)	0.069
Pot cooked coffee without filter	1.00	0.90 (0.40-2.01)	0.39 (0.17-0.90)	0.48 (0.18-1.28)	0.33 (0.09-1.18)	0.062

*Adjusted for age, study year, body mass index, systolic blood pressure, education, occupational physical activity (light, moderate, and active), walking or cycling to/from work (0, 1-29, and ≥30 minutes per day), leisure time physical activity (low, moderate, and high), cigarette smoking (never, past, and current smoking of 1-19 or ≥20 cigarettes per day), alcohol consumption (0, 1-100, 101-300, and >300 g per week), and tea consumption (none, 1-2, and ≥3 cups per day) and sex.

†This analysis only includes Finnrisk study years of 1987 and 1992.

5.1.4 *Type of the coffee and risk of type 2 diabetes*

The type of coffee consumed by the participants was assessed in the surveys of 1987 and 1992. More than 80% of the Finnish coffee consumers used filtered coffee at the baseline. The likelihood ratio test was applied to determine the interaction between the type of coffee and the amount of coffee on the risk of type 2 diabetes. No interaction occurred between the type of coffee and the amount of coffee for the risk of type 2 diabetes (P>0.1 for trend). Men and women who drank pot-boiled coffee, without filtering, showed a similar inverse trend in the risk of type 2 diabetes in comparison with people who drank filtered coffee. After multivariate adjustment including the amount of coffee consumed, however, men who mainly drank pot-boiled coffee showed a 2.9 times higher risk for the development of diabetes compared with men who drank filtered coffee. This association was also observed among men and women combined (Table 12).

Table 12. ***Hazard ratios for the development of type 2 diabetes by different type of coffee consumption according to the sex and age* (study I).***

	No. of new cases		Person-years		**Risk ratio**	
	Filtered coffee	**Pot cooked coffee without filter**	**Filtered coffee**	**Pot cooked coffee without filter**	**Filtered coffee**	**Pot cooked coffee without filter**
Men	40	36	25410	6915	1.00	2.86 (1.76-4.63)
Age <50 years	17	11	16001	2923	1.00	3.89 (1.65-9.21)
Age ≥50 years	23	25	9409	3992	1.00	2.72 (1.49-4.96)
Women	38	26	29462	7943	1.00	1.30 (0.76-2.24)
Age <50 years	6	4	18032	3067	1.00	2.11 (0.45-9.99)
Age ≥50 years	32	22	11430	4876	1.00	1.29 (0.72-2.33)
Men and women combined†	78	62	54871	14858	1.00	2.04 (1.43-2.92)
Age <50 years	23	15	34034	5990	1.00	2.71 (1.33-5.53)
Age ≥50 years	55	47	20837	8868	1.00	1.87 (1.24-2.82)

*Adjusted for age, study year, body mass index, systolic blood pressure, education, occupational physical activity (light, moderate, and active), walking or cycling to/from work (0, 1-29, and ≥30 minutes per day), leisure time physical activity (low, moderate, and high), cigarette smoking (never, past, and current smoking of 1-19 or ≥20 cigarettes per day), alcohol consumption (0, 1-100, 101-300, and >300 g per week), tea consumption (none, 1-2, and ≥3 cups per day), and coffee consumption (0-2, 3-4, 5-6, 7-9, ≥10 cups per day). This analysis only includes Finnrisk study years of 1987 and 1992.

†Also adjusted for sex.

5.2 *Coffee consumption and glycemic markers*

Analyses in the study **II** (Table 13) revealed that coffee consumption was significantly and inversely associated with fasting insulin among men and with 2-hour glucose levels among women in age- and study year-adjusted analysis.

Table 13. Baseline ***characteristics of study prticipants aged 45-64 years by glucose status and sex* (study II)***

	Men			Women		
	Normal glucose†	**Impaired glucose regulation†**	**P value‡**	**Normal glucose†**	**Impaired glucose† regulation**	***P* value for trend‡**
n	811	240		1180	203	
Age (year)	54.7 ± 5.9	55.2 ± 5.9	0.29	55.1 ± 6.0	56.2 ± 5.9	0.015
BMI (kg/m^2)	27.2 ± 3.4	29.0 ± 4.0	<0.001	27.1 ± 4.7	30.4 ± 5.6	<0.001
Systolic blood pressure (mmHg)	144 ± 19	147 ± 20	0.011	142 ± 21	149 ± 21	<0.001
Diastolic blood pressure (mmHg)	88 ± 11	90 ± 12	0.017	84 ± 11	87 ± 10	0.001
Fasting glucose (mg/dl)	91 ± 11	109 ± 10	<0.001	89 ± 11	105 ± 12	<0.001
2-hour glucose (mg/dl)	94 ± 23	132 ± 33	<0.001	96 ± 20	148 ± 26	<0.001
Fasting insulin (μU/ml)	8.4 ± 5.1	10.6 ± 6.5	<0.001	8.1 ± 5.1	13.1 ± 8.4	<0.001
Daily coffee consumption (cups)	4.9 ± 3.0	4.4 ± 2.9	0.028	4.1 ± 2.2	3.7 ± 2.1	0.013
Education (year)	9.4 ± 3.8	9.5 ± 3.3	0.67	9.6 ± 3.5	9.0 ± 3.5	0.032
Low occupational physical activity (%)	55.1	59.2	0.27	53.2	63.1	0.009
Low leisure time physical activity (%)	21.2	24.6	0.29	26.5	33.7	0.041
Walking or cycling to/from work <30 minutes (%)	86.1	89.6	0.19	78.6	80.6	0.58
Tea drinker (%)	40.4	42.1	0.65	42.8	47.3	0.25
Alcohol drinker (%)	62.8	71.3	0.017	41.4	35.0	0.089
Current smoking (%)	27.5	32.1	0.17	12.4	11.3	0.73

*Values are presented as mean ± SD or percentage.

†Normal glucose, fasting glucose <110 mg/dl and 2-hour glucose <140 mg/dl; impaired glucose regulation, fasting glucose 110-125 mg/dl and/or 2-hour glucose 140-199 mg/dl.

‡T-test for continuous variables and chi-square test for categorical variable

After adjustment for all potential confounding factors (age, study year, BMI, systolic blood pressure, education, occupational, commuting, and leisure time physical activity, alcohol and tea drinking, and smoking), coffee consumption was significantly and inversely associated with fasting glucose, 2-hour plasma glucose, and fasting insulin among both men and women. For men and women together, we found that an increment of one cup of coffee per day was associated with 0.29 mg/ml lower fasting glucose, 1.16 mg/ml lower 2-hour glucose, and 0.24 µU/ml lower fasting insulin (Table 14).

Table 14. *Linear regression analysis of the association between coffee consumption and glucose and insulin levels (study* ***II****)*

	Regression coefficient (95% CI)		
Coffee consumption, cups/day	**Fasting glucose**	**2-hour glucose**	**Fasting insulin**
Men			
Adjustment for age and study year	-0.18 (-0.39 to 0.03)	-0.55 (-1.14 to 0.04)	-0.14 (-0.24 to -0.03)‡
Multivariate adjustment*	-0.33 (-0.56 to -0.10)‡	-0.64 (-1.28 to -0.01)‡	-0.22 (-0.33 to -0.12)‡
Women			
Adjustment for age and study year	-0.10 (-0.35 to 0.15)	-1.34 (-1.99 to -0.68)‡	-0.10 (-0.23 to 0.03)
Multivariate adjustment*	-0.26(-0.50 to -0.01)‡	-1.77 (-2.43 to –1.12)‡	-0.26 (-0.38 to -0.14)‡
Men and women combined†			
Adjustment for age and study year	-0.15 (-0.31 to 0.01)	-0.89 (-1.33 to -0.45)‡	-0.12 (-0.21 to -0.04)‡
Multivariate adjustment*	-0.29 (-0.45 to -0.12)‡	-1.16 (-1.61 to -0.70)‡	-0.24 (-0.31 to -0.16)‡

*Adjusted for age, study year, body mass index, systolic blood pressure, education, occupational and leisure time physical activity, walking or cycling to/from work, cigarette smoking, alcohol and tea consumption.

†Adjusted also for sex.

‡P value <0.05.

After the adjustment for all confounding factors, coffee consumption was significantly and inversely associated with impaired fasting glucose, impaired glucose regulation, and hyperinsulinemia among both men and women. A significant inverse association also occurred between coffee consumption and isolated impaired glucose tolerance among women. Coffee consumption as a continuous variable showed that an increment of one cup of coffee per day was associated with a 10% lower risk of impaired fasting glucose, an 8% lower risk of isolated impaired glucose tolerance, a 9% lower risk of impaired glucose regulation, and an 11% lower risk of hyperinsulinemia if both men and women were combined (Table 15).

Table 15. ***Adjusted odd ratio of the association between coffee consumption and hyperglycaemia and hyperinsulinemia (study II)***

	Odd ratios (95% CI)			
Coffee consumption, cups/d	**Impaired fasting glucose***	**Isolated impaired glucose tolerance***	**Impaired glucose regulation***	**Hyperinsulinemia**
Men	N=978	N=884	N=1051	N=1051
Adjustment for age and study year	0.94 (0.88-1.00)	0.97 (0.89-1.06)	0.95 (0.90-1.01)	0.96 (0.91-1.01)
Multivariate adjustment†	0.90 (0.83-0.98)	0.97 (0.87-1.06)	0.92 (0.87-0.99)	0.89 (0.83-0.95)
Women	N=1277	N=1286	N=1383	N=1383
Adjustment for age and study year	0.94 (0.85-1.04)	0.91 (0.83-1.01)	0.92 (0.86-0.99)	0.97 (0.92-1.03)
Multivariate adjustment†	0.88 (0.79-0.98)	0.89 (0.80-0.99)	0.89 (0.82-0.96)	0.88 (0.82-0.94)
Men and women combined‡	N=2255	N=2170	N=2434	N=2434
Adjustment for age and study year	0.94 (0.89-0.99)	0.94 (0.89-1.01)	0.94 (0.90-0.98)	0.96 (0.93-1.00)
Multivariate adjustment†	0.90 (0.85-0.96)	0.92 (0.86-0.99)	0.91 (0.87-0.96)	0.89 (0.85-0.93)

*Using normal glucose tolerance, fasting glucose <110 mg/dl and 2-hour glucose <140 mg/dl as reference group in the analysis of hyperglycaemia; impaired fasting glucose, fasting glucose 110-125 mg/dl; isolated impaired glucose tolerance, 2-hour glucose 140-199 mg/dl and fasting glucose <110 mg/dl; impaired glucose regulation, fasting glucose 110-125 mg/dl and/or 2-hour glucose 140-199 mg/dl; hyperinsulinemia; sex- and study year-specific quartile 4 of fasting insulin.

†Adjusted for age, study year, body mass index, systolic blood pressure, education, occupational and leisure time physical activity, walking or cycling to/from work, cigarette smoking, alcohol and tea consumption.

‡Adjusted also for sex.

5.3 *Coffee, diabetes & cardiovascular mortality*

In the study **V** (Table 16), during the average follow-up of 20.8 years, 1,471 deaths were recorded, of which 909 were encoded as CVD, 598 as CHD, and 210 as the stroke.

Table 16. ***Baseline characteristics of participants with type 2 diabetes by volume of coffee consumption* (study V)***

	Daily coffee consumption, cups				*P* value
	0-2	**3-4**	**5-6**	**≥7**	**for trend**
Number of participants	644	1041	1356	796	
Women, %	47.2	58.6	54.6	38.3	
Age, years	48.8±11.3	49.7±10.3	49.4±10.3	47.8±9.9	<0.001
Body mass index, kg/m^2	29.4±5.1	29.8±5.1	30.0±5.2	29.9±5.2	0.07
Systolic blood pressure, mmHg	152±23	153±24	153±24	153±24	>0.2
Diastolic blood pressure, mmHg	93±13	93±13	93±13	92±13	>0.2
Total cholesterol, mmol/l	6.3±1.3	6.5±1.3	6.6±1.4	6.6±1.3	0.001
Education, years	8.3±3.9	8.0±3.6	7.5±3.2	7.2±3.1	<0.001
Low physical activity, %	22.7	18.4	15.6	13.1	<0.001
Alcohol drinkers, %	43.0	38.1	38.4	44.0	0.2
Tea drinkers, %	58.1	39.9	21.3	11.4	<0.001
Current smoking, %	22.8	20.7	25.5	45.9	<0.001

*Values represent means±SD or percentages unless otherwise indicated. Adjusted for age, sex, and study year.

Age-, sex-, and study year-adjusted HRs in participants who drank 0-2, 3-4, 5-6, and ≥7 cups of coffee daily were 1.00, 0.79, 0.72, and 0.79 for total mortality, 1.00, 0.81, 0.75, and 0.79 for CVD mortality, 1.00, 0.81, 0.77, and 0.71 for CHD mortality, and 1.00, 0.75, 0.62, and 0.90 for stroke mortality. After further adjustment for other co-factors (BMI, systolic blood pressure, total cholesterol, education, physical activity, alcohol and tea consumption, and smoking), these inverse associations became stronger and significant for total mortality, CVD mortality, and CHD mortality, but became no longer significant for stroke mortality (Table 17).

Table 17. ***Hazard ratios of total, CVD, CHD, and stroke mortality by volume of coffee consumption among participants with type 2 diabetes (study V)***

	Daily coffee consumption, cups				*P* value for trend
	0-2	3-4	5-6	≥7	
Total mortality					
Number of deaths	247	384	529	311	
Person-years	11,772	20,551	29,927	17,406	
Hazard ratios, model 1[a]	1.00	0.79 (0.67-0.93)	0.72 (0.62-0.85)	0.79 (0.67-0.94)	0.001
Hazard ratios, model 1[b]	1.00	0.78 (0.66-0.92)	0.69 (0.59-0.82)	0.72 (0.60-0.87)	<0.001
Hazard ratios, model 1[c]	1.00	0.77 (0.65-0.91)	0.68 (0.58-0.80)	0.70 (0.59-0.85)	<0.001
CVD mortality					
Number of deaths	146	241	337	185	
Hazard ratios, model 1[a]	1.00	0.81 (0.66-0.99)	0.75 (0.62-0.92)	0.79 (0.63-0.98)	0.04
Hazard ratios, model 1[b]	1.00	0.80 (0.65-0.99)	0.73 (0.59-0.90)	0.74 (0.58-0.94)	0.02
Hazard ratios, model 1[c]	1.00	0.79 (0.64-0.97)	0.70 (0.57-0.86)	0.71 (0.56-0.90)	0.006
CHD mortality					
Number of deaths	96	160	231	111	
Hazard ratios, model 1[a]	1.00	0.81 (0.63-1.05)	0.77 (0.61-0.98)	0.71 (0.54-0.94)	0.09
Hazard ratios, model 1[b]	1.00	0.79 (0.61-1.03)	0.73 (0.57-0.95)	0.65 (0.48-0.88)	0.04
Hazard ratios, model 1[c]	1.00	0.78 (0.60-1.01)	0.70 (0.54-0.90)	0.63 (0.47-0.84)	0.01
Stroke mortality					
Number of deaths	35	54	69	52	
Hazard ratios, model 1[a]	1.00	0.75 (0.49-1.14)	0.62 (0.41-0.94)	0.90 (0.59-1.40)	0.08
Hazard ratios, model 1[b]	1.00	0.79 (0.51-1.22)	0.66 (0.43-1.03)	0.94 (0.58-1.52)	0.15
Hazard ratios, model 1[c]	1.00	0.77 (0.50-1.19)	0.64 (0.41-0.99)	0.90 (0.56-1.45)	0.12

[a]Adjusted for age, sex, and study year.

[b]Adjusted for age, sex, study year, education, alcohol and tea consumption, and smoking status.

[c]Adjusted for age, sex, study year, body mass index, systolic blood pressure, total cholesterol, education, alcohol and tea consumption, and smoking status.

When coffee consumption was examined as a continuous variable, the multivariate-adjusted HRs associated with an increment of one cup of coffee per day were 0.96 for total mortality, 0.97 for CVD mortality, 0.96 for CHD mortality, and 0.99 for stroke mortality. The multivariate-adjusted HRs in people drinking 3 cups of coffee or more were 0.72 for total mortality, 0.73 for CVD mortality, 0.71 for CHD mortality, and 0.73 for stroke mortality compared to people drinking 0-2 cups of coffee daily (Table 18).

Table 18. ***Hazard ratios (95% CIs) of total, CVD, CHD, and stroke mortality by volume of coffee as continuous variable and by different volume of coffee (≥3 cups versus 0-2 cups) among participants with type 2 diabetes* (study V)***

	Coffee as continuous variable		≥3 cups versus 0-2 cups of coffee daily	
	Hazard ratios (95% CIs)	***P* value for trend**	Hazard ratios (95% CIs)	***P* value for trend**
Total mortality	0.96 (0.94-0.99)	0.002	0.72 (0.62-0.83)	<0.001
Cardiovascular mortality	0.97 (0.94-0.99)	0.02	0.73 (0.61-0.89)	0.001
Coronary heart disease mortality	0.96 (0.93-0.99)	0.02	0.71 (0.57-0.90)	0.005
Stroke mortality	0.99 (0.92-1.05)	>0.2	0.73 (0.92-1.05)	0.12

*Adjusted for age, sex, study year, body mass index, systolic blood pressure, total cholesterol, education, alcohol and tea consumption, and smoking status.

A non-significant inverse association was found between tea consumption and mortality for total, CVD, and CHD, but not stroke mortality (Table 19).

Table 19. ***Hazard ratios (95% CIs) of total, CVD, CHD, and stroke mortality by volume of tea consumption among participants with type 2 diabetes***

	Daily tea consumption, cups			***P* value for trend**
	0	**1-2**	**≥3**	
Total mortality				
Number of deaths	1056	296	119	
Person-years	55,944	17,436	6276	
Hazard ratios, model 1[a]	1.00	0.88 (0.77-1.00)	0.92 (0.76-1.11)	0.13
Hazard ratios, model 1[b]	1.00	0.84 (0.74-0.97)	0.85 (0.70-1.04)	0.03
Hazard ratios, model 1[c]	1.00	0.84 (0.73-0.96)	0.87 (0.71-1.06)	0.03
CVD mortality				
Number of deaths	652	186	71	
Hazard ratios, model 1[a]	1.00	0.89 (0.76-1.05)	0.88 (0.69-1.12)	>0.2
Hazard ratios, model 1[b]	1.00	0.86 (0.72-1.02)	0.82 (0.63-1.06)	0.10
Hazard ratios, model 1[c]	1.00	0.85 (0.71-1.00)	0.85 (0.66-1.10)	0.11
CHD mortality				
Number of deaths	430	126	42	
Hazard ratios, model 1[a]	1.00	0.92 (0.75-1.12)	0.78 (0.57-1.07)	>0.2
Hazard ratios, model 1[b]	1.00	0.87 (0.70-1.07)	0.72 (0.52-1.00)	0.09
Hazard ratios, model 1[c]	1.00	0.85 (0.69-1.05)	0.76 (0.54-1.05)	0.13
Stroke mortality				
Number of deaths	143	44	23	
Hazard ratios, model 1[a]	1.00	0.97 (0.69-1.37)	1.28 (0.82-1.98)	>0.2
Hazard ratios, model 1[b]	1.00	0.97 (0.68-1.39)	1.23 (0.77-1.95)	>0.2
Hazard ratios, model 1[c]	1.00	0.96 (0.67-1.37)	1.26 (0.79-2.00)	>0.2

[a]Adjusted for age, sex, and study year.

[b]Adjusted for age, sex, study year, education, alcohol and tea consumption, and smoking status.

[c]Adjusted for age, sex, study year, body mass index, systolic blood pressure, total cholesterol, education, alcohol and coffee consumption, and smoking status.

6. DISCUSSION

6.1 *Coffee consumption and risk of type 2 diabetes*

This study revealed clear evidence for an inverse and graded association between coffee consumption and type 2 diabetes (Studies **I**, **III**, **IV)**. Habitual coffee drinkers, both middle aged men and women, in the highest category of coffee consumption had the least risk of developing diabetes. The expanded analyses in the studies **III** and **IV** (larger sample size & longer follow up period) observed the same finding as study **I**. Based on the published data, the Finnish population drinks more coffee than other populations (World Resources Institute 2003), so siting enough power to determine the risk of type 2 diabetes at high levels of coffee consumption.

6.1.1 *Coffee consumption and potential diabetes risk factors*

Coffee, obesity, BMI, & type 2 diabetes It is well known that obesity is associated with impaired glucose tolerance and development of type 2 diabetes (Cairney and Wade 1998; WHO reports 2000; 1994). Excess fat accumulation may lead to increased insulin resistance, thus development of type 2 diabetes is predictable (Lewis et al. 2002). Weight control by lifestyle intervention has resulted in improvement in insulin and glucose control in obese people (Finnish Diabetes Prevention Program Research Group 2002; Diabetes Prevention Group 2001; Ross et al. 2000). Greenberg et al. found that caffeinated and decaffeinated coffees were independently associated with weight loss, which may imply that both caffeine and noncaffeine compounds in coffee may help people decrease body weight (Greenberg et al. 2006; Greenberg et al. 2005). This idea is supported by the recent results of a larger prospective study, which found that increases in caffeine, coffee, and decaffeinated coffee intake were associated with smaller weight gains over a 12-year period (Lopez-Garcia et al. 2006a).

Coffee, physical activity, & type 2 diabetes Sedentary life style and physical inactivity have been shown to be associated with obesity (King et al. 2001) and on the opposite side physical activity prevents it. One of the major recommendations to obese or nonobese people at risk of developing type 2 diabetes would be to keep up their physical activity or to be more physically active. Although weight reduction can be achieved by controlled diet and energy intake, physical activity will help energy expenditure and secure weight loss maintenance (Borg et al. 2004).

Coffee, alcohol consumption, & type 2 diabetes Alcohol consumption has been found to be associated with the risk of type 2 diabetes in some epidemiological studies (Howard et al. 2004). Moderate alcohol consumption appears to be associated with a reduced risk for diabetes, whereas some evidence suggests that heavy alcohol consumption may be associated with an increased risk (Djoussé et al. 2007; Howard et al. 2004). Therefore, the observed effect of coffee consumption on the risk of diabetes may be influenced by alcohol consumption. The present study, however,

indicated that the inverse association between coffee consumption and the risk of type 2 diabetes persisted in both alcohol drinkers and non-drinkers.

Coffee, type 2 diabetes, & joint association with potential risk factors Study **III** evaluated in detail the joint association of coffee consumption and diabetes risk factors including physical activity, BMI, and alcohol consumption, on the risk of development of type 2 diabetes. The inverse and graded association between coffee consumption and the risk of type 2 diabetes was consistent in both men and women, in the subjects with any joint levels of physical activity and BMI, and in alcohol drinkers and non-drinkers. Particularly interesting was the finding that among obese and inactive people, coffee consumption halved the risk of type 2 diabetes.

The type of the coffee and type 2 diabetes In a previous study on the Finnish population (Reunanen et al. 2003), no association between the coffee consumption and incidence of type 2 diabetes was observed. One possible explanation for the different results is that at the time of their baseline survey, in 1973 and 1977, most Finnish individuals drank pot-boiled coffee. At the end of the 1960s, 75% of the Finnish population drank boiled coffee (Aro 1990) but by 1987 this proportion had decreased to 24%, although, 69% drank filtered coffee (Pietinen et al 1990). Although, however, we were able to determine the type of the coffee consumed in our surveys in 1987, and 1992, there was no interaction effect between the type of coffee and amount of coffee on the risk of type 2 diabetes in either men or women. Nevertheless, a significant, almost 3-fold, increase occurred in the risk of diabetes among men who drank pot-boiled coffee compared to men who drank filtered coffee.

Coffee consumption & type 2 diabetes in women The observed inverse association between coffee consumption and the risk of type 2 diabetes seems to be stronger in women than in men, although, the sex-interaction was not statistically significant. Previous studies have revealed that caffeine may be positively associated with plasma estrogen, plasma estradiol, and sex hormone-binding globulin levels and inversely related with testosterone among postmenopausal women (Nagata et al. 1998; Ferrini et al. 1996). In addition, phytoestrogens may have beneficial effects on patients with diabetes. The phytoestrogen content of coffee and effects of caffeine on the hormonal level may explain the effects of coffee on the risk of diabetes in women. Nevertheless, in most populations, the prevalence of type 2 diabetes is lower in pre-menopausal women than in men (DECODE Study Group 2003; Qiao et al. 2003).

6.2 *Coffee consumption and glycemic markers*

The major finding in study **II** was an inverse association between coffee consumption and several markers of "glycemia and diabetes". Coffee consumption was associated with lower values of fasting glucose, 2-hour glucose and fasting insulin among non-diabetic subjects. Coffee consumption was significantly and inversely associated with impaired fasting glucose, impaired glucose regulation, and hyperinsulinemia among both men and women and with isolated

impaired glucose tolerance only among women. Nevertheless, the sex difference on the effect of coffee drinking on glycemia was not statistically significant.

Our findings were consistent with the observed inverse association between habitual coffee consumption and postload glucose level in Dutch (van Dam et al. 2004), Japanese (Yamaji et al. 2004) and Swedish (Agardh et al. 2004) populations. This data revealed that coffee may affect postload glucose as well as fasting glucose (preload) metabolism. Coffee consumption, however, was more strongly associated with decreased postload glucose concentrations than fasting plasma glucose. Postload glucose regulation is an important issue not only in the glucose metabolism and development of diabetes but also in the developing of the most serious complications in diabetic patients. This issue needs to be investigated in more detail at the *intestinal*, *hepatic*, and the *peripheral delivery stages* of the glucose metabolism. Because up to 30 minutes after the ingestion of the glucose load, the increase in plasma glucose concentration can be attributed solely to the increased delivery into the circulation as a result of increased intestinal absorption in response to the load. Once this has peaked, the peripheral metabolism of glucose (i.e. delivery into muscle and fat tissue in addition to hepatic glucose metabolism) will have a significant affect on overall plasma concentrations and thus, any differences seen cannot solely be attributed to the affects on absorption (Frayn 1996).

Lower fasting insulin values and the lower risk of hyperinsulinemia among coffee consumers in this study may be interpreted as an improvement in insulin sensitivity by coffee consumption at the *peripheral delivery stage* of the glucose metabolism. The acute affects of caffeine on decreasing insulin sensitivity have also been reported (Keijzers et al. 2002). One may believe, however, that these affects might be modified during a long period of coffee consumption as it has already seen in cardiovascular effects (Denaro et al. 1991) and glucose metabolism may follow a different pattern among heavy and chronic coffee consumers. Also, the beneficial effects of the other components of the coffee other than caffeine, on insulin sensitivity should be considered. In a recent cross-sectional study, Ärnlöv et al. investigated the association between coffee consumption and both insulin sensitivity and insulin secretion. They determined the insulin sensitivity index by hyperinsulinemic euglycemic clamp and found that both coffee and tea consumption improved insulin sensitivity (Arnlov et al. 2004).
Despite the relatively good correlation between the fasting plasma insulin and insulin sensitivity derived from the hyperinsulinemic euglycemic clamp, measures of fasting plasma insulin explain no more than 50% of the variability in insulin action seen in non-diabetic subjects (Yeni-Komshian et al. 2002; Laakso 1992). This is because plasma insulin levels not only depend on insulin sensitivity, but also on a complex interplay between insulin secretion, distribution, and degradation (Ferrannini and Mari 1998). The measurement of plasma insulin concentration after an overnight fast, however, seems to be one of the most practical ways to give some estimate of insulin resistance from a clinical perspective (Haffner et al. 1992; Zavaroni et al. 1989; Despres et al. 1996; Fontbonne et al. 1991) and very high plasma insulin values usually reflect the presence of insulin resistance. Low, or normal, insulin values are probably effective on postload glucose concentration.

6.3 *Potential mechanisms underlying the protective effects of coffee consumption on glycemic markers and type 2 diabetes*

Although the biological mechanism behind the inverse association between coffee consumption and the risk of type 2 diabetes is unknown, several putative mechanisms can be proposed.

Coffee in its metabolic process Coffee contains many compounds, other than well-known caffeine, which may have the potential to influence glucose metabolism in each of its metabolic stages. One of the possible mechanisms is the *intestinal stage* inhibition or retardation of the action of α−Glucosidase by chlorogenic acid. The inhibition of this enzyme is an effective approach to control hyperglycemia (Matsui et al. 2001). It has also been reported that chlorogenic acid inhibits glucose transporters (Na^+ -dependent glucose transporter) at the same stage (Kobayashi et al. 2000). In addition, coffee may also influence the secretion of gastrointestinal peptides such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), both are known for their glucose lowering effects (Meier et al. 2001; Nauck et al. 1993). At the *hepatic stage* reduced Glucose-6-phosphatase (Glc-6-Phase) hydrolysis or its inhibition by the chlorogenic acid may reduce plasma glucose output leading to reduced plasma glucose concentration (Andrade-Cetto et al. 2001; Arion et al. 1997; Youn et al. 1986; Newgard et al. 1984).

Caffeine and Energy Expenditure Caffeine has been found to increase the resting metabolic rate in both lean and obese individuals (Horton and Geissler 1996; Bracco et al. 1995; Astrup et al. 1990). This thermogenic effect of caffeine may overcome the energy imbalance accompanied by unfavorable lifestyle and improve glucose homoeostasis.

Coffee Consumption and Iron Stores Te mechanism of the observed inverse association between coffee consumption and diabetes might be, at least in part, due to the inhibition of iron absorption by polyphenol compounds present in coffee (Mascitelli et al. 2007). Higher body iron stores are associated with an increased risk for diabetes (Jiang et al. 2004); moreover the induction of iron deficiency in impaired glucose tolerant subjects has been shown to improve insulin sensitivity (Facchini and Saylor 2002).

Further details on other possible mechanism have been discussed within the discussions of the individual studies.

6.4 *Coffee, GGT & type 2 diabetes*

Study **IV** evaluated the association between coffee consumption and type 2 diabetes, based on baseline GGT levels. Despite observing the same inverse association between coffee and type 2 diabetes, the results were influenced by baseline GGT levels. At high GGT levels (≥75% percentile), coffee drinking was inversely associated with type 2 diabetes in women and both sexes combined, but this association was non-significant in men.

***Serum GGT level & type 2 diabetes*:** The strong association between the serum concentration of GGT and the risk for the development of impaired fasting glucose or type 2 diabetes has already been documented (Perry et al. 1998). Recent prospective studies showed that the risk of the metabolic syndrome and type 2 diabetes increases with increasing serum GGT level (Nakanishi et al. 2004; Lee et al. 2003a; Lee et al. 2003b; Nakanishi et al., 2003; Perry et al. 1998) and GGT has been suggested as an important risk indicator for developing type 2 diabetes. Despite the apparent relation between the GGT levels and alcohol intake (Sharper et al. 1985; Skinner et al. 1984), the association between GGT concentration and type 2 diabetes has been found to be independent of alcohol intake (Lee et al. 2003a; Lee et al. 2003b). Also among subjects with high normal GGT levels, BMI, and age are strong risk factors for incident type 2 diabetes (Lee et al. 2003a; Lee et al. 2003b). A previous study based on almost same study population as our present study revealed that a higher serum GGT concentration within normal ranges was directly associated with the increased risk of type 2 diabetes (Lee et al. 2004).
Present analysis has now indicated that the risk of type 2 diabetes among people with high normal serum GGT levels is not necessarily increased, but actually decreased among habitual coffee consumers.

***Coffee consumption & serum GGT level*:** The relation between coffee consumption and GGT concentration, which has been studied previously (Kono et al. 1994; Casiglia et al. 1993; Nilssen et al. 1990), revealed an inverse association between coffee consumption and GGT level. The effects of regular daily coffee consumption on liver enzymes were studied in a large number of subjects from the general population by Casiglia et al. (1993). They found that in coffee drinkers, GGT and other liver enzymes (alkaline-amino transferase and alkaline phosphatase) were lower than in non-coffee-drinking subjects or in those consuming less than 3 cups daily. In addition, a study by Esposito et al. (2003) revealed that moderate coffee consumption significantly increased the plasma glutathione (GSH) level among healthy subjects. It is well known that with increasing GSH levels, GGT concentration decreases consequently (Zhang et al. 2005).

***Proposed underlying mechanism*:** Better knowledge of GGT and its important physiologic role in pathological conditions is necessary in order to explain our present findings. It is known that GGT is a plasma membrane enzyme facilitating the transport of extracellular GSH into most types of cells and that GSH is the major intracellular nonprotein thiol defence against free radicals (oxidative stress) (Karp et al. 2001; Kugelman et al. 1994). The accumulation of free radicals, elevated oxidative stress, leads to a raise of the GGT level in order to modify the existing oxidative stress by reproducing GSH. The γ-glutamyl cycle, involving GGT, is the major pathway by which cells utilize extracellular GSH for the de novo synthesis of intracellular GSH (Griffith et al. 1978). This is the main way that membrane GGT is protecting cells from oxidative stress (Karp et al. 2001). The elevation of GGT could be the expression of excess deposition of fat in the liver (hepatic steatosis), and/or may reflect inflammation (Malnik et al. 2003; Hotalamsligil et al. 2003; Marchesini et al. 2001). Both express the presence of oxidative stress and its major role in pathological conditions such as inflammation, malignant diseases, aging, cardiovascular disease (Droge et al., 2002), and in pathophysiology of diabetes (Rosen et al. 2001; West et al. 2000; Haluzik et al. 2000). A decrease in antioxidant capacity has been observed in the plasma of diabetic patients (Rosen et al. 2001; Haluzik et al. 2000; Maxwell et al. 1997; Jones et al. 1988) and evidence from a number of experimental studies revealed that the formation of free radicals and the presence of oxidative stress is a direct consequence of

hyperglycemia (Ceriello et al 1999; Graier et al. 1996; Diedrich et al. 1994). So, we know that coffee contains many compounds which consequently may have the potential to influence the glucose metabolism process to prevent hyperglycemia and oxidative stress (Sections 2.2.2.1, 5.2).

***Finally*,** increased GGT levels, for any reason, are related to excess oxidative stress and excessive oxidative stress may play a role in initiating the development of type 2 diabetes. Thus, the increasing frequency of the disease in people with high GGT levels may be expected (Lee et al. 2003a). In our study, however, we found fewer cases of incident diabetes among habitual coffee consumers with high normal GGT levels indicating stronger protective effects of coffee at these levels. It may be interpreted that the antioxidant capacity of coffee may be more activated at a particular oxidative stress level at which it is helpful in preventing diabetes in subjects who are more susceptible to develop diabetes. A recent study by Ruhl et al., investigated the association of coffee and tea consumption on chronic liver diseases (Ruhl et al. 2005), supports these findings. They found a lower risk associated with higher levels of coffee and/or tea consumption only in persons who are at higher risk for liver disease from heavier alcohol intake, overweight, diabetes, or high iron saturation. These findings suggest hypotheses for future research.

6.5 *Coffee Consumption & CVD mortality among diabetic patients*

Our large prospective study found an inverse association between coffee consumption and the risk of total, CVD and CHD mortality among patients with type 2 diabetes. These associations were independent of age, BMI, systolic blood pressure, total cholesterol, physical activity, alcohol drinking, and smoking.

Type 2 diabetes and CVD risk It is well known that types 2 diabetes is a potential risk factor for all-cause, CVD, and stroke mortality (Hu et al. 2005a; Hu et al. 2005b; DECODE Study Group 2001; Wei M et al. 1998; Lehto et al. 1996). A dose-response relationship between level of the hyperglycaemia and both CVD deaths and all-cause mortality has been observed (Wei et al. 1998).

Coffee consumption and CVD risk The relation between coffee consumption and CVD has been extensively studied. Although coffee consumption has frequently been related to unhealthy lifestyle behavior, or in the other words well known CVD risk factors such as smoking and sedentary lifestyle, the relation of coffee consumption with development or progression of CVD has remained controversial. Most of the previous cohort studies found no evidence of any positive association between coffee consumption and risk of CHD (Willett et al. 1996; Kawachi et al. 1994; Greenland 1993; Myers and Basinski 1992) while a Scottish cohort study (Woodward M 1999) revealed that higher coffee consumption was associated with the lower risk of CVD only among men. In a study of a Finnish cohort, Kleemola et al. observed a lower risk of nonfatal MI in men with higher coffee consumption (>7 cups/d) (Kleemola 2000). They also found a slight increase in CHD mortality in the same group. Some other, mostly case-control studies, found a positive association (Cornelis et al. 2006; Happonen et al. 2004). The most recent data from Iowa Women's Health Study cohort (Andersen et al. 2006) revealed that

consumption of 1-3 cups of coffee per day would be protective on total and CVD death. Two other large cohort studies (Lopez-Garcia et al. 2006b) revealed no adverse association between coffee consumption and risk of developing CHD.

Coffee consumption & CVD risk factors The effects of coffee and caffeine on the certain risk factors for CVD, such as blood pressure and serum cholesterol, have also been reported. In a long-term prospective study, Klag et al. found that coffee drinking is associated with the small increase in blood pressure (Klag et al. 2002) and Hartley et al. found that modest doses of caffeine may increase blood pressure (Hartley et al. 2002). Another study by Winkelmayer et al. (2005), however, demonstrated that consumption of coffee in women is not associated with the increased the risk of developing hypertension. Coffee reportedly raises lipid parameters, however, it is clearly evidenced that filtered coffee is free of two cholesterol raising ingredients, Cafestol and Kahweol (Weusten-Van der Wouw et al. 1994). Moreover, the positive effect of chronic intake of caffeine on serum lipids has been reported (Du et al. 2005). Previously, we found a graded inverse association between coffee consumption and type 2 diabetes (Tuomilehto et al. 2004) and now this large cohort study established a reduced risk of total, CVD, and CHD mortality among type 2 diabetic patients who drank two or more cups of coffee daily. This association was relatively strong and not affected by the other confounding or effect modifying factors that were included in the analyses. After the adjustment for the other CVD potential risk factors, the result actually became somewhat stronger.

Proposed underlying mechanism It has been suggested that oxidative stress is the common pathogenic factor leading to insulin resistance, β-cell dysfunction, impaired glucose tolerance, and finally to type 2 diabetes (Ceriello and Motz 2004). Furthermore, this mechanism has been implicated as the underlying cause of both the macrovascular and microvascular complications associated with type 2 diabetes (Brownlee 2001; Rösen et al. 2001; Pieper and Gross 1998; Tesfamariam 1994). Blood glucose fluctuation during postprandial glycaemic excursions, in people with impaired glucose tolerance or type 2 diabetes, may significantly contribute to oxidative stress even more than chronic elevation of blood glucose (Hirsh and Brownlee 2005). Experimental studies demonstrate that the formation of free radicals and presence of oxidative stress is a direct consequences of hyperglycaemia (Graier et al. 1996; Diedrich et al. 1994; Tesfamariam et al. 1990) and postprandial hyperglycaemia is a significant predictor of CVD both in non-diabetic subjects and diabetic patients (The DECODE Study Group 2003; Qiao et al. 2002; DECODE Study Group 2001).
Thus, preventing hyperglycemia means protecting cells from further progression to diabetes and its complications. Previous studies, from diverse countries, revealed that higher coffee consumption was consistently associated with a lower prevalence of hyperglycemia and in particular, coffee consumption seems to lower post-prandial hyperglycemia (Van Dam et al. 2004; Yamaji et al. 2004). We also found lower fasting insulin values and the lower risk of hyperinsulinemia among coffee consumers with long term exposure, which may consequently be interpreted as an improvement in insulin sensitivity by coffee consumption to prevent hyperglycemia and oxidative stress. It has been also suggested that coffee may interfere in different stages of glucose metabolism and glycemic regulation regarding preventing hyperglycemia (Bidel et al. 2006).

6.6 *Methodological considerations*

This study is based on the FINRISK database. Compared with other studies the FINRISK Study has many advantages, such as a large number of baseline measurements of risk factors and comprehensive follow-up data. It is carried out in a relatively homogeneous population. After the baseline data collections and examination, each subject has been followed by computerized record linkage using the unique national personal identification (PI) code assigned to every Finnish resident, to various national data bases. These include the Causes of Death Register (Statistics Finland), the National Hospital Discharge Registry (Stakes) since 1968, the National Social Insurance Institute's (KELA) Drug register since 1964, and the National Cancer Registry since 1953. Thus, it would be possible to have a complete ascertainment of the subjects for the follow-up and obtain information about changes in their health status after the baseline examination.

The results of these large prospective studies have extended the results of the other countries published during recent years. The prospective design, relatively long follow-up, and almost complete information on potential confounders are definite advantages of this study. Several issues regarding exposure classification, outcome measure, and residual confounding, however, should be considered when interpreting the results.

Coffee exposure in this study is assessed using a questionnaire that collects information regarding the number of cups of coffee consumed daily. Since relying on self-reports, this study may be susceptible to bias resulting from inaccurate reporting. The misclassification of exposure, however, is most probably not systematically related to the outcome and vice versa. Therefore, it should not have caused biased results, but may only weaken the observed association.
No information available from study questionnaire elicited the size of the coffee cup. It has been speculated, however, that the size of the coffee cup in Finland was approximately 100-125 ml at the time of the baseline data collections. Nevertheless, the test for trend did not depend on cup size, since coffee consumption was included as a continuous variable. Depending on the population the cup size may vary and it can not be standardized (Debry 1994). Thus, the caffeine content of coffee can vary and people who drink more may consume weaker coffee than people who drink only one or two cups per day. The type of coffee and the brewing methods to prepare coffee are other issues for which not much information is available.

Validity of exposure measurement is a key problem in epidemiological research (Armstrong et al. 1992). Based on the validation study of the dietary questionnaire carried out in subgroups of the study population, however, the correlations between the dietary questionnaire and food records for coffee were 0.89 in men and 0.85 in women (Paalanen et al. 2006).

Differences in the metabolism of compounds in coffee may cause variation in the exposure for an individual. For instance, N-acetyltransferase 2 plays a significant role in the metabolism of caffeine (Carrillo and Benitez 2000). A polymorphism in N-acetyltransferase 2 gene may affect the individual exposure to the metabolites of caffeine (Nakajima et al. 1999; Sachse et al. 1999). In addition, it has been reported that cigarette smoking increases caffeine clearance by inducing the activity of the cytochrome P450 1A2 isoform, which accounts for 95% of the metabolism of

caffeine, and thus the level of the caffeine in smokers is lower than that in nonsmokers given the same level of caffeine consumption (Joeres R et al., 1988).

Avoiding drinking coffee due to a preexisting chronic disease may be a concern as a potential bias. We, however, excluded participants with reported diabetes, CHD, or stroke at baseline and this bias is unlikely to influence our results.

A lack of the glucose tolerance test at baseline and follow-up surveys could have caused us to miss some cases of asymptomatic and diet-treated diabetes although the clinical diagnosis of diabetes from the hospital discharge register may in part avoid this potential under-diagnosis. With all precaution measures, however, it was possible that some of the diabetic subjects were among subjects who are classified as non-diabetic and it may became a source of bias in this study. To avoid this potential bias, additional analyses were performed excluding cases of type 2 diabetes, which occurred during the first four years of follow up but the results did not change.

Finally, the affects of residual confounding due to measurement error in the assessment of confounding factors, or some unmeasured factors including coffee additives (sugar and/or milk) and several dietary factors (such as the intake of the whole grain, the intake of fiber, magnesium, calcium, sodium, saturated and polyunsaturated fat, glycaemic load of the diet and total energy intake) can not completely be excluded (Hu et al. 2005c; Steyn et al. 2004; Song et al. 2004).

6.7 *Future prospects*

The potentially preventable nature of type 2 diabetes has been evidenced by the implementation of lifestyle measures, such as weight control and exercise. In many of the borderline cases of type 2 diabetes, the clinical appearance of the disease and consequent complications may be delayed or prevented by diet and exercise for many years. It may show the efficacy of the dietary behavior in preventing or slowing the progression the disease. More or less, coffee has been included in the dietary menu of most of the people and it seems to be helpful in overall glucose metabolism. We believe, however, that these protective effects cannot be solely achieved by coffee drinking without considering the other lifestyle measures. In addition, many people stop or lessen coffee drinking due to aging, digestive problems, or some other health related reasons and consequently the overall incidental rates have not changed.

Although habitual coffee consumption seems to be a safe and useful lifestyle behavior in type 2 diabetes, which has been confirmed by published data from diverse countries, better knowledge of the components of the coffee, human consumption, and bioavailability is still needed in order to properly evaluate the true role of coffee in type 2 diabetes. Eventually, research in this area should lead to dietary recommendations optimized for specific population groups at risk of type 2 diabetes.

7. CONCLUSIONS

To our knowledge this is the first time that the relation between coffee and type 2 diabetes has been completely reviewed. These finding were based on large cohort studies with long term follow-up and cross-sectional studies.
Following conclusions related to the study objectives were drawn based on the main findings:

1. A strong and graded inverse relationship exists between coffee consumption and the risk of type 2 diabetes among Finnish men and women, a population with the highest coffee consumption in the world.
Expansion of the analysis with a larger sample size and longer follow up period confirmed the previous results and this association was observed regardless of the levels of physical activity, BMI, and alcohol consumption. Among obese and inactive people drinking seven or more cups of coffee daily halved the risk of type 2 diabetes.

2. In the cross-sectional analysis, we found that coffee has favorable affects on the markers of glycemia. An inverse association between coffee consumption and several markers of glycemia particularly fasting glucose, 2-hour glucose, and fasting insulin among non-diabetic subjects, was an extremely important finding.

3. The inverse association between coffee consumption and the incident type 2 diabetes is modified by serum GGT levels. The mechanism of this association has not yet been clarified. Nevertheless, the antioxidant activity of coffee by interfering in the glucose metabolism process is the most probable mode of action, since a high GGT level is a marker of oxidative stress.

4. A consistent inverse relationship exists between coffee consumption and the risk of total, CVD, and CHD mortality among patients with type 2 diabetes. The complex components of coffee with antioxidant activity and potential to interfere in the different stages of glucose metabolism to control hyperglycemia are the most probable mechanisms.

Final conclusion: These data will complement the gradually growing body of data that provides more evidence for the overall beneficial effects of coffee consumption in relation to type 2 diabetes.

ACKNOWLEDGMENTS

This study was carried out in the Diabetes Unit, Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute (KTL) and the Department of Public Health, Faculty of Medicine, University of Helsinki.

I wish to thank KTL for providing me with research facilities and for the privilege of using the extensive datasets gathered here. I also wish to thank the Department of Public Health for the same reason. Financial support from both the Doctoral Program in Public Health and the Juho Vainio Foundation is highly appreciated.

I have been very fortunate to have two excellent supervisors. Without Professor Jaakko Tuomilehto's genuine interest in and enthusiasm for the topic this study would never have been started. I have always felt welcome to discuss with him any problems related to this project or other topics with him. He generously provided grants for proceeding and presenting the study. Professor Jaakko Kaprio has continually found time for reading and commenting on my manuscripts. His valuable detailed comments have always helped to create better versions. Finally, it has been a great honor working with these two top scientists in this field and I hope this study shows a little of my deep appreciation.

The official referees of the dissertation, docent Sari Voutilainen and Professor Paul Knekt are gratefully acknowledged for their careful work and constructive criticism that helped to clarify the manuscript during the final steps.

I wish to thank all my co-authors, who kindly spent time to read and comments on the manuscripts. I am also grateful to all the other people who have worked for years creating such excellent data sources.

I warmly thank all my colleagues in the National Public Health Institute by accepting me and never turning down my request for help.

I would like to share my joy with and dedicate this work to my dear wife Dr. Giti Khalighi-Sikaroudi for her incredible support, and my sons Ali and Kami for their patience during all these times.

Finally, I deeply praise all the men and women who participated in the projects, creating excellent sources of data for writing this thesis.

Helsinki, May 2008
Siamak Bidel

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