Turun yliopisto
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SEDENTARY BEHAVIOUR AND HEALTH

With Special Reference to Obesity and Fatty Liver in Early Midlife

The Cardiovascular Risk in Young Finns Study

Harri Helajärvi

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Lauri “Tahko” Pihkala (1888-1981):

“*Lift, bus, and in-house toilet*
– the start of the destruction of the public health!”

ABSTRACT

Harri Helajärvi

Sedentary behaviour and health with special reference to obesity and fatty liver in early mid-life. The Cardiovascular risk in Young Finns Study.

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Background: Physical inactivity and positive energy balance pose a risk to health. They increase the risk of obesity and associated non-communicable diseases. Recently, also sedentary behaviour has been associated with obesity and non-communicable diseases. Nevertheless, it has been unclear which type of sedentary behaviour is the most harmful. It is also unknown whether the relationship of sedentary behaviour with obesity is truly independent of other factors, for example physical activity and diet. Longitudinal data are limited, and the direction of causality and the mechanism of action are still unknown.

Aims: The aim of this study was 1) to identify the type of sedentary behaviour having the strongest association with obesity, 2) to explore the causal relationship of sedentary behaviour and weight increase, and 3) to additionally, investigate the relationship of sedentary behaviour with fatty liver. These were studied in cross-sectional and/or longitudinal settings using data from the Cardiovascular Risk in Young Finns Study. Special emphasis was put on the evaluation of a wide range of other lifestyle factors and risks for obesity and fatty liver.

Subjects: 2,060 subjects (aged 33-50 years in 2011, of which 55 % were female) from the Cardiovascular Risk in Young Finns Study participating in follow-ups in 2001, 2007, and 2011.

Measures: Self-reported time spent in various types of sedentary behaviour (I), or TV viewing time (I-III). Measured body weight, height and waist circumference (I-III), and genetic variants for high BMI (I). Fasting plasma concentrations of gamma-glutamyltransferase enzyme and triglycerides, calculated Fatty Liver Index (based on gamma-glutamyltransferase and triglyceride concentration, BMI and waist circumference), and the amount of intrahepatic fat measured with ultrasound (III). Self-reported leisure-time physical activity and active commuting, occupational physical activity, energy intake, diet, alcohol consumption, smoking, socioeconomic status, and sleep duration as possible confounders were considered (I-III).

Results: TV viewing is the sedentary behaviour type that has the strongest association with obesity. Sedentary behaviour (TV viewing) precedes weight increase, and not the other way around. Sedentary behaviour (TV viewing) is associated with increased risk of fatty liver.

Conclusions: Sedentary behaviour (especially high TV viewing time) is associated with increased risks of obesity and fatty liver. Intervention studies are needed to assess whether reduction of TV time would prevent obesity and fatty liver.

TIIVISTELMÄ

Harri Helajärvi

Runsas istuminen ja terveys – yhteys aikuisiän lihavuuteen ja rasvamaksaan. Lasten Sepelvaltimotaudin Riskitekijät (LASERI) -tutkimus.

Turun yliopisto, Lääketieteellinen tiedekunta, Terveysliikunta, Turun yliopiston kliininen tohtoriohjelma, Sydäntutkimuskeskus ja Paavo Nurmi -keskus

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Tausta: Vähäinen liikunta ja positiivinen energiatasapaino ovat terveysriskejä, jotka lisäävät lihavuutta sekä siihen liittyviä elintapasairauksia. Viime aikoina myös runsaan istumisen on todettu liittyvän lihavuuteen ja elintapasairauksiin. On epäselvää, mihin toimintoihin liittyvä istuminen on haitallisinta. Ei ole myöskään selvää, miten riippumaton runsaan istumisen ja lihavuuden sekä elintapasairauksien yhteys on muista tekijöistä, esimerkiksi liikunnasta ja ravitsemuksesta. Pitkittäisaineistoja on hyvin vähän, eikä syy-seuraussuhteen suuntaa tai vaikutustapaa tunneta.

Tavoitteet: Tämän tutkimuksen tarkoituksena oli tutkia, 1) mihin toimintoihin liittyvällä istumisella on haitallisin yhteys lihavuuteen ja 2) selvittää runsaan istumisen sekä painon nousun syy-seuraussuhdetta. 3) Lisäksi selvitettiin runsaan istumisen yhteyttä rasvamaksaan. Tutkimus tehtiin suomalaisessa Lasten Sepelvaltimotaudin Riskitekijät (LASERI) –aineistossa sekä poikittais- että pitkittäisasetelmissa. Erityistä huomiota kiinnitettiin lukuisiin muihin lihavuuden ja maksan rasvoittumisen riskiä lisääviin elintapoihin ja tekijöihin.

Tutkimushenkilöt: 2,060 tutkittavaa (iältään 33-50 vuotiaita vuonna 2011, joista 55 % oli naisia) Lasten Sepelvaltimotaudin Riskitekijät –tutkimuksesta, jotka ottivat osaa vuosien 2001, 2007 ja 2011 seurantoihin.

Mittaukset: Itse raportoitu, eri toimintoihin liittyvään istumiseen (I) tai TV:n katseluun käytetty aika (I-III). Mitattu kehon paino, pituus (I-III), ja vyötärönympärys (I-III) sekä suurta painoindeksiä ennustavat geenivariantit (I). Paastoverinäytteestä määritetyt gammaglutamyylitrasferaasi-entsyymin ja triglyseridien pitoisuudet ja näistä sekä painoindeksistä ja vyötärönympäryksestä laskettu rasvamaksaindeksi sekä ultraäänikuvauksella mitattu maksan rasvoittumisen aste (III). Itse raportoitu vapaa-ajan ja työmatkaliikunta, työn fyysinen kuormittavuus, energian saanti sekä ravitsemuksen laatu, alkoholin käyttö, tupakointi, sosioekonominen asema ja unen määrä otettiin huomioon mahdollisina vaikuttavina muuttujina (I-III).

Tulokset: TV:n katseluun liittyvä istuminen on voimakkaimmin yhteydessä lihavuuteen. Runsas istuminen (TV:n katselu) edeltää painon nousua, eikä päinvastoin. Runsas istuminen (TV:n katselu) on yhteydessä kohonneeseen rasvamaksan riskiin.

Päätelmät: Runsas istuminen (erityisesti runsas TV:n katselu) on yhteydessä suurentuneeseen lihavuuden ja rasvamaksan riskiin. Interventiotutkimuksia tarvitaan selvittämään, voidaanko TV:n katsomista vähentämällä pienentää lihavuuden syntymistä ja maksan rasvoittumista.

CONTENT

ABSTRACT **4**

TIIVISTELMÄ **5**

LIST OF ORIGINAL PUBLICATIONS **8**

ABBREVIATIONS **9**

1. INTRODUCTION **10**

2. REVIEW OF LITERATURE **12**

2.1. Sedentary behaviour 12
2.1.1. Definition 12
2.1.2. Subjective data collection 12
2.1.3. Objective data collection 13
2.1.4. Factors influencing sedentary behaviour 13
2.1.5. Sedentary behaviour and health 14
2.1.5.1. Observational studies 15
2.1.5.2. Intervention studies 15
2.1.6. Breaking of sedentary bouts 16
2.2. Obesity 16
2.2.1. Definition and measurement 16
2.2.2. Environment and genetics 17
2.2.3. Obesity and sedentary behaviour 17
2.3. Fatty liver 18
2.3.1. Definition and measurement 18
2.3.2. Fatty liver and sedentary behaviour 18

3. AIMS OF THE STUDY **20**

4. SUBJECTS & METHODS **21**

4.1. Subjects 21
4.2. Sedentary behaviour (I-III) 23
4.3. Body mass index and waist circumference (I-III) 24
4.4. GGT and triglyceride concentration, FLI (III) 24
4.5. Liver ultrasound (III) 24
4.6. Possible confounders (I-III) 25
4.6.1. Physical activity (I-III) 25
4.6.2. Diet (I-III) 26
4.6.3. Alcohol, smoking, sleep, and socioeconomic status (I-III) 27
4.6.4. Genetic variants (I) 27

5. DATA ANALYSIS 28
5.1. Cross-sectional analyses (I, III) 28
5.2. Longitudinal analyses (II, III) 28

6. RESULTS 30
6.1. Obesity (studies I, II) 30
6.2. Causal relationship (study II) 31
6.3. Fatty liver (study III) 32

7. DISCUSSION 35
1.1. Summary of the main findings 35
7.1. The role of TV viewing 35
7.2. Possible confounders 36
7.2.1. Diet 36
7.2.2. Genetic predisposition 36
7.3. Methodological considerations 36
7.3.1. Strengths 36
7.3.2. Limitations 37
7.4. Implications for future studies 37
7.4.1. Metabolic pathways and effects on target organs 37
7.4.2. Intervention studies 38
7.4.3. Data collection 38
7.4.4. Causal relationship 38
7.4.5. Genetics 39
7.4.6. Making behaviour change 39

8. CONCLUSIONS AND IMPLICATIONS 40

9. ACKNOWLEDGEMENTS 41

10. REFERENCES 45

ORIGINAL PUBLICATIONS 51

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by Roman numerals I-III:

I. Heinonen I, Helajärvi H, Pahkala K, Heinonen OJ, Hirvensalo M, Pälve K, Tammelin T, Yang X, Juonala M, Mikkilä V, Kähönen M, Lehtimäki T, Viikari J, Raitakari OT. Sedentary behaviours and obesity in adults: the Cardiovascular Risk in Young Finns Study. BMJ Open 2013;3:002901.doi:10.1136/bmjopen-2013-002901

II. Helajärvi H, Rosenström T, Pahkala K, Kähönen M, Lehtimäki T, Heinonen OJ, Oikonen M, Tammelin T, Viikari JSA, Raitakari OT. Exploring causality between TV viewing and weight change in young and middle-aged adults. The Cardiovascular Risk in Young Finns Study. PLoS ONE 2014;9(7): e101860. doi:10.1371/journal.pone.0101860

III. Helajärvi H, Pahkala K, Heinonen OJ, Oikonen M, Tammelin T, Hutri-Kähönen N, Kähönen M, Lehtimäki T, Mikkilä V, Viikari J, Raitakari OT. TV viewing and fatty liver in early midlife. The Cardiovascular Risk in Young Finns Study. Ann Med 2015;47(6):519-526. DOI: 10.3109/07853890.2015.1077989. Epub 11 Sep 2015

ABBREVIATIONS

AUC	Area under curve
BAI	Body adiposity index
BMI	Body mass index
DXA	Dual-energy X-ray absorptiometry
FLI	Fatty liver index
GGT	Gamma-glutamyl transferase enzyme
LAP	Lipid accumulation product
MET	Metabolic equivalent
NAFLD	Non-alcoholic fatty liver disease
OLETF rat	Otsuka Long-Evans Tokushima Fatty rat
PA	Physical activity
PAI	Physical activity index
SES	Socioeconomic status
SNP	Single nucleotide polymorphism
uFLI	Ultrasonographic fatty liver index
WH-ratio	Waist-to-hip ratio
WHt-ratio	Waist-to-height ratio

1. INTRODUCTION

The importance of healthy lifestyle is widely known, and the intelligent human being has developed various ways to ease and improve the way of living. This has, indeed, helped people to live longer and stay healthier, but on the other side, the modern, easy lifestyle has started to pose new, unanticipated risks.

Earlier, occupational physical activity (PA) used to keep people more active physically, but nowadays – due to physically less demanding work – people try to find PA in their spare time (Levine JA 2015). Occupations traditionally regarded as physically demanding have turned into half-automated and physically significantly less active, even sedentary (Church TS et al. 2011). At the same time, on the population level, also leisure-time PA has decreased (Levine JA 2015). The reduced leisure-time and occupational PA and lowered energy expenditure at work (Church TS et al. 2011), but also changes in diet and possible increase in energy intake (Putnam J et al. 2002, Rasmussen LB et al. 2012) have played a role in the development of the current obesity pandemic. Obesity causes a rapidly increasing health and cost burden (Swinburn BA et al. 2011). It is estimated to count for 2-6% of total health care costs in many countries (WHO 2007), and already 39% of the global population aged 18 is reported to be overweight and 13% obese (WHO 2015).

The prevalence of non-alcoholic fatty liver (NAFLD) has increased in parallel with obesity (Demir M et al. 2015), and fatty liver is associated with increased risk of obesity (Clark JM et al. 2002, Wiechowska A et al. 2007). In addition, fatty liver is associated with metabolic syndrome (Stefan N et al. 2008), insulin resistance (Adams LA et al. 2007), type 2 diabetes (Angulo P 2002), and cardiovascular disease (Targher G et al. 2010).

Physical inactivity increases the risk of non-communicable diseases (Matheson GO et al. 2013) including obesity (Ross SE et al. 2015) and NAFLD (Hickman IJ et al. 2004, Harrison SA et al. 2007, St George A et al. 2009). PA guidelines have been created to help people stay physically active and to promote health (WHO 2010(a)). Nevertheless, physical inactivity has become the 4th leading risk factor for mortality globally (WHO 2010(b)). It is estimated to cause about 5 million premature deaths a year, which is as many as caused by cigarette smoking (Lee IM et al. 2012). Due to shortened distances secondary to urbanization, increased passive transportation, and rapid increase in technology usage (TV, computer, mobile phones and other mobile technology) people have to engage themselves less physically (Levine JA 2015). Time spent passively, and literally sitting, has increased. Daily inactivity makes already about ¾ of the waking time (Husu P et al. 2014). Therefore, previous recommendations for health enhancing PA (150 minutes of moderate PA, or 75 minutes of vigorous PA a week combined with muscular exercises twice a week) (Physical Activity Guidelines Advisory Committee 2008, O'Donovan G et al. 2010, Swedish Professional Association for Physical Activity 2011), although still relevant, may no more suffice in the new, passive, and obesogenic world.

Although the change in the environment and the easier way of living have been in many ways helpful and beneficial to health, physically inactive lifestyle - with its rapid increase - has introduced health risks that are somewhat poorly understood. Sedentary lifestyle has been independently associated with obesity, type II diabetes, metabolic syndrome, cardiovascular

diseases, and premature mortality (Dunstan DW et al. 2012, Wilmot EG et al. 2012). This may decrease public health and increase health care costs, and has raised the need to better understand the complex relationship between sedentary behaviour and cardiometabolic diseases. The need for more robust data on sedentary behaviour and its impact on human health is key to gain a better understanding on the risks associated with sedentary lifestyle.

This study in Finns was conducted in order to identify the sedentary behaviour(s) that have the strongest associations with obesity, to evaluate the increase in body weight across time, to study the causal relationship between sedentary behaviour and increase in body weight. Furthermore, the aim of this study was to investigate fatty liver risk in individuals with high sedentary time taking into consideration a large number of other known risks for obesity and fatty liver, e.g. leisure-time and occupational PA, diet, and alcohol.

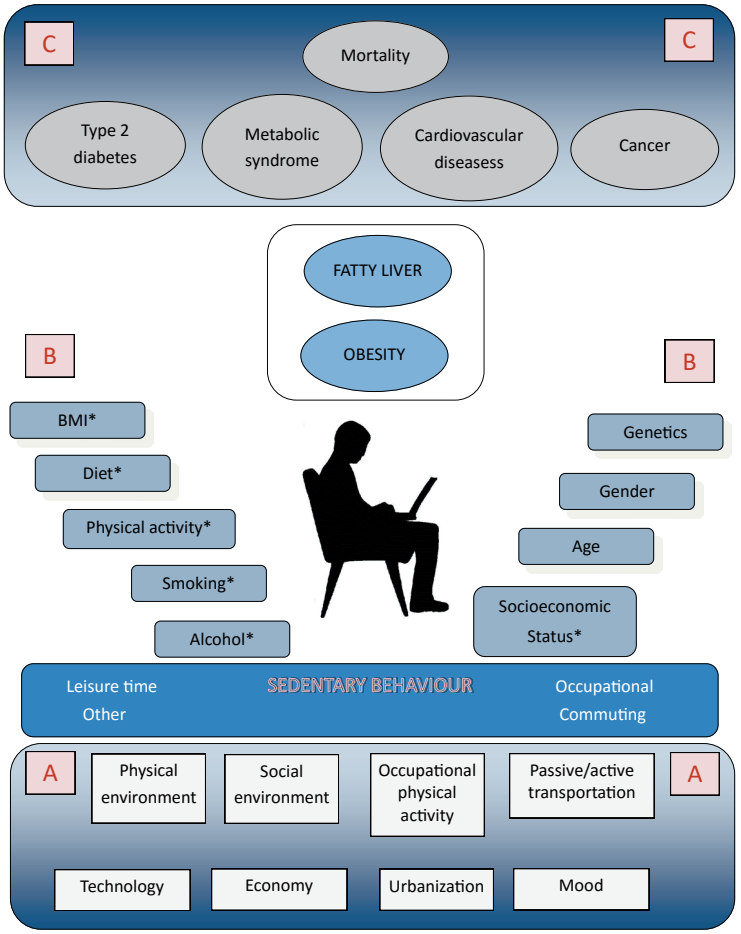

Figure 1. The landscape of modern era sedentary behaviour and other behavioural or physical factors having an impact on health. The lowest level (A), describes the promoters and preventers of sedentary behaviour. The intermediary level (B), links sedentary behaviour together with other lifestyle and risk factors possibly associated with obesity, fatty liver, and increased risk of non-communicable diseases. The non-communicable diseases and premature mortality (all-cause and cardiometabolic) most often associated with sedentary behaviour are outlined on the highest level (C).

* = modifiable factors having an impact on non-communicable disease risk

2. REVIEW OF LITERATURE

2.1. Sedentary behaviour

2.1.1. Definition

Sedentary behaviour is defined as an immobile state of the body in a sitting or reclined position resulting in an energy expenditure close to the resting metabolic rate, i.e. 1-1.5 METs (MET=Metabolic Equivalent, equaling an oxygen consumption of 3.5ml/kg). This may occur at any time of the day, i.e. during leisure-time, commuting, at work, and at other times. When objectively measured with accelerometers, movement is converted by sensors into electrical signals (counts). Sedentary time is often defined as PA below 100 counts per minute (Matthews CE et al. 2008). Sedentary time may be assessed based on overall sedentary time, or selected type(s) of sitting.

2.1.2. Subjective data collection

Sedentary time used for investigational purposes can be self-reported or objectively measured (Atkin AJ et al. 2012). Self-reporting has been the traditional way of collecting information on PA, and also sedentary behaviour. In general, self-reporting is good for collecting data on the amount of *various types* of sedentary behaviour, but it can also be used to collect information on e.g. *circumstances* in which the sitting or PA took place and *moods* associated with them (Clemes SA et al. 2012). On the other hand, subjectively collected data may be somewhat biased due to under- or overreporting (Clemes SA et al. 2012). The bias - and subsequent errors - vary depending on the target population and questions posed, time gap between the activity and data collection, and actual data collected (Clemes SA et al. 2012, Olsson SJ et al. 2015). The more time elapses between any behaviour and subjective data collection, the more biased the data may be due to recall issues (Matthews CE et al. 2012). As far as sedentary behaviour is concerned, general questions on overall, daily sedentary time provide less accurate data than questions on a specific sitting type, e.g. TV viewing (Clemes SA et al. 2012). TV viewing and computer use are sedentary behaviours that can be recorded with relatively good accuracy with questionnaires (Clark BK et al. 2009, Otten JJ et al. 2009). This may be due to e.g. their frequency, specificity and regularity. Sometimes the combined time spent in front of the computer or TV monitor, 'screen time', is recorded. Sometimes 'total sedentary time' is calculated to combine all daily time used on activities performed in a sitting or reclined position. Of all sedentary behaviour types, TV viewing time has most frequently been associated with the adverse health outcomes seen with sedentary behaviour (Williams DM et al. 2008).

One challenge for subjective data collection is the fact that some of the activities traditionally regarded as sedentary may be done alongside with other sedentary - or physical - activities (e.g. listening to music while reading - or even during household work, and during physical exercise). Recording all these sedentary behaviour types in such situations separately would result in inappropriate overestimation of sedentary time, or classification of concurrent PA inadvertently as sedentary behaviour.

2.1.3. Objective data collection

Objective measurement of sedentary behaviour means collecting factual data on time spent immobile, in this case sitting. With objective data collection various PA intensities (vigorous, moderate, and light intensity PA) and types can be distinguished more accurately than with subjective reporting, but the accuracy varies depending on the technology used (Reilly J et al. 2008). Collecting PA data objectively has been reported to yield lower values than when using subjective data collection methods (Hagströmer M et al. 2007). All objective activity monitors may not be able to distinguish between sitting, lying down and standing, or even between sedentary behaviour and low intensity PA (Pedišić Ž et al. 2015). This has limited their use in sedentary behaviour studies, but the latest technology and use of multidirectional accelerometers together with inclinometers have significantly reduced this limitation (Bonomi AG et al. 2012). The meta-analyses of objectively collected data may be challenging, as data collection frequency and definitions (=count limits per minute used to distinguish between various types of physical activity / inactivity, and counts per unit time, i.e. epochs) vary between studies (Reilly J et al. 2008). In addition, data collection methods and device locations (e.g. waist vs. wrist worn devices) vary from one study to another (Hildebrand M et al. 2014). Also lack of appropriate and comparable motion and step detection algorithms based on the collected data can have an impact on data quality (Reilly J et al. 2008, Cain KL et al. 2013, Scholes et al. 2014). Another, recently introduced objective method of collecting PA and sedentary behaviour data are shorts that measure muscular electromyographic activity (Tikkanen O et al. 2013).

Overall, more accurate and frequent data collection has become possible with new technology, which increases data quality, but at the same time this results in a significant increase in the amount of data. This poses a challenge from the data storage and analysis point of view. On the other hand, with pure objective data collection one can never fully record e.g. the context and the moods associated with an activity, be it PA or sedentary behaviour.

2.1.4. Factors influencing sedentary behaviour

The environment, both physical and social, play a significant role in promoting or preventing human behaviour (Levine JA 2015).

The social influences can be caused by the shared or non-shared (or unique) environment (Eysenck HJ 1990). Shared environment is the one that is shared by siblings reared in the same family. This includes such variables as socioeconomic status and parent education. Non-shared environment is the environment unique to the individual, that includes variables like peer group (Eysenck HJ 1990). The influences of environment on our behaviours vary depending on phases of life (de Geus EJC et al. 2014), i.e. during childhood and adolescence the shared environment is more important, but the significance of the non-shared environment increases with age. The motivational aspects may also be sex-specific (Allender S et al. 2006). In addition, PA, and especially physical inactivity, track as we age (Telama R et al. 2014, Fogelholm M et al. 1999).

The physical environment either promotes or prevents sedentary behaviour and PA (de Geus EJC et al. 2014). To a large extent, the modern environment is built and designed to promote physical inactivity and sitting instead of an active lifestyle (Levine JA 2015). This concerns all age groups and sedentary behaviour in different contexts, i.e. at daycare, schools, workplace, public places and home (van Uffelen JG et al. 2010, Levine JA 2015). Also increased commuting with cars and reduced distances in an urban surrounding reduce PA and increase sedentary time (Levine JA 2015).

Mood is an important moderator of behaviour, as shown by studies where depressive mood reduced PA and made an individual choose a more passive lifestyle (Zhai L et al. 2014).

Genetics play a role also, but behaviours are complex and polygenic, i.e. they are influenced by multiple genes (Eysenck HJ 1990, Reiss D 1997, Bouchard TJ Jr et al. 2003, Aaltonen S et al. 2013). Genetics may make individuals react to PA physiologically in different ways, which is shown in a study of 60 subjects. In this study, 8.4% had an adverse exercise-induced change in fasting insulin concentration, 12.2% in systolic blood pressure, 10.4% in serum triglyceride concentration, and 13.3% in HDL-cholesterol concentration (Bouchard C et al. 2012). In the same study, about 7% of the study subjects had adverse responses for two or more risk factors. The experience of PA, or physical inactivity, may also vary depending on genes (de Geus EJC et al. 2014). Different genes may be involved in promoting PA or physical inactivity (Stubbe JH et al. 2006, de Vilhena e Santos DM et al. 2012). On the other hand, behaviours themselves may modify gene function (Mustelin L et al. 2009), and according to recent studies epigenetic changes, may also be transferred from one generation to another (Horsburgh S et al. 2015).

Also high body mass, fat mass and waist circumference may predict sedentary time as described by Ekelund U et al. (2008), suggesting that heavier individuals are prone to be physically less active, but this was seen only in the younger cohorts of their study.

2.1.5. Sedentary behaviour and health

Sitting and stationary positions have already for a longer time been known to increase the risk of musculoskeletal disorders (Pope MH et al. 2002, Luttman A et al. 2003). More recently, sedentary behaviour has been associated with an increased risk of obesity and non-communicable diseases, i.e. type 2 diabetes, metabolic syndrome, cardiovascular diseases, and also all-cause and cardiovascular mortality, regardless of other risks and lifestyle, like PA and diet (Dunstan DW et al. 2012, Wilmot EG et al. 2012). Traditionally, cardiometabolic diseases have been estimated to develop within few decades, but in younger generations they may progress much more rapidly (Anstee QM et al. 2013). In addition to the increased disease risks, an earlier disease development would increase health costs. According to recent studies, individuals spending most of their time in an upright position (=leading a more active way of living) may live longer than those that have a primarily sedentary lifestyle (Katzmarzyk PT 2014).

2.1.5.1. Observational studies

Observational studies, many of them cross-sectional in design, have produced the bulk of currently available sedentary behaviour data. These include direct associations with obesity and type 2 diabetes (Hu FB et al. 2003), metabolic syndrome (Edwardson CL et al. 2012), certain cancers (Schmidt et al. 2014, Ukawa S et al. 2014), and all-cause and cardiovascular mortality (Kim Y et al. 2013).

TV viewing, of all sedentary behaviour types, has been most frequently associated with adverse health outcomes (Grontved A et al. 2011), but some uncertainty still remains how important other sedentary behaviours and overall daily sitting are. It is also unclear whether the actual sedentary behaviour (e.g. TV viewing) drives the negative health outcomes, and what the role of other unhealthy habits associated with it is – e.g. unhealthy eating during TV viewing seen especially in the younger generation (Pearson N et al. 2011).

Recent investigations on reduced and less diverse human microbiota and its associations with increased obesity, non-communicable diseases and allergies (von Hertzen L et al. 2015) have raised an interesting, possible link between sedentary behaviour and health: Increased sedentary time might also reduce human microbiota by increasing time spent indoors and reducing exposure to the environment and its biodiversity (von Hertzen L et al. 2015).

The cumulative data suggest that sedentary behaviour has an independent, negative impact on health, but data comparison between studies, and drawing conclusions from different studies is challenging due to various study designs and different variables evaluated. In addition, the independent nature of sedentary behaviour and the type of sedentary behaviors mostly responsible for the detected associations are still questioned. Also the mechanisms of action remain unknown. In addition, due to the nature and design of most observational studies, the causal relationship of the detected associations remains unclear.

2.1.5.2. Intervention studies

Intervention studies on sedentary behaviour include settings where e.g. TV viewing time or computer use time has been reduced and subsequent weight change, energy consumption, or cardiometabolic markers have been measured. These are described in more detail below.

Interventions to reduce sedentary behaviour may have been delivered through a variety of settings, e.g. family/home, occupation, community, school, and clinic or research centre, and they can be a) informative, b) behavioural, c) environmental, or d) socially supportive in nature (Biddle SJH et al. 2014). In a randomized clinical trial of 36 adults, a 50% reduction in TV viewing time decreased the BMI with an increase in objectively measured energy expenditure without a change in energy intake (Otten JJ et al. 2009). Reduction in 70 children's TV and computer time in a randomized clinical trial resulted in a decreased BMI related to the decrease in energy intake, but not to the change in PA (Epstein LH et al. 2008). In 25 intervention studies of imposed, uninterrupted sedentary behaviour ($\leq$7 days) consistent, moderate quality evidence of deletarious changes in insulin

sensitivity, glucose tolerance and triglyceride concentration were seen (Saunders TJ et al. 2012). Different combinations of increased PA, or reduced sitting, and diet interventions were evaluated for their effectiveness in weight reduction in an American study: Decreased sedentary time and increased consumption of fruits and vegetables was more effective in weight reduction than a) increased PA and increased consumption of fruits and vegetables, b) increased PA and decreased consumption of saturated fat, or c) decreased sedentary time combined with decreased consumption of saturated fat (Spring B et al. 2012). In a randomized controlled intervention study in overweight, elderly individuals (N=49, age 68 years) reduction of sedentary time increased the length of blood cell telomeres associated with longevity (Sjögren P et al. 2014).

Overall, interventions to reduce sedentary time have resulted in changes in cardiometablic markers that are in line with findings seen in observational studies, but long-term effects are still to a large extent unclear. According to a randomized clinical trial interventions at work place can also reduce occupational sedentary time (Parry S et al 2013).

2.1.6. Breaking of sedentary bouts

Sedentary behaviour is not only about the total amount of sitting. Also the duration of individual sitting bouts is of importance.

In an observational study in 168 subjects (mean age 53.4 years) with objective sedentary behaviour and PA data collection, breaking prolonged sitting bouts, independently from the total amount of sedentary time and moderate-to-vigorous PA, was positively associated with waist circumference, BMI, triglyceride concentration and plasma 2-hour glucose concentration during an oral glucose tolerance test (Healy GN et al. 2008).

Interrupting postprandial sedentary time with short bouts of light- or moderate-intensity walking in a randomized controlled trial resulted in lowering of glucose and insulin levels (Dunstan DW et al. 2012). In a cross-over intervention study in overweight/obese individuals (N=8, ages 45-65 years), breaking postprandial sitting resulted in increased expression of genes involved in anti-inflammatory and anti-oxidative pathways, and carbohydrate and lipid metabolism (Latouche C et al. 2013). Data from studies on breaking of prolonged sitting are summarized in a recent review article (Benatti FB et al. 2015).

2.2. Obesity

2.2.1. Definition and measurement

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. These may be defined as body mass exceeding a predefined weight limit or high percentage of body fat. As body weight is highly related to height, body mass index (BMI, kg/m^2) is used to better define normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9) or obesity (BMI 30 or higher). On the population level, the average BMI tends to increase with age to approximately the age of 65, and then starts to decrease (Visscher TLS et al. 2000). In addition, waist circumference (Janssen I et al. 2004), waist-to-hip ratio (WH-ratio) (WHO 1999, Stevens J et al. 2010, Lear SA et al. 2010), waist-to-height ratio (WHt-ratio)

(Ashwell M et al. 1996) and Body Adiposity Index (BAI) based on hip circumference and height (Bergman RN et al. 2011) have been introduced as estimates of body composition. Modern technology used to more accurately measure the fat content and its locations include MRI, biomedical impedance analysis, and the golden standard, dual-energy X-ray absorptiometry (DXA) scan (Lee SY et al. 2008).

2.2.2. Environment and genetics

Obesity, like PA and sedentary behaviour, is affected by environmental and genetic factors, but the basic mechanism behind the gain in body weight is positive energy balance (i.e. energy intake exceeds energy expenditure). Some diseases, like hypothyreosis, may also increase body weight. Thirty-one genetic variants increasing the risk of high BMI have been identified (Speliotes EK et al. 2010), but not only the existence or non-existence of selected genes or their variants matter. Differences in phenotypes due to lifestyle have been shown in studies comparing genetically identical twins (Waller K et al. 2010). The physically active one of a twin pair has been shown to be leaner than the sedentary one, and PA reduces the importance of genetic predisposition to develop high BMI and waist circumference (Mustelin L et al. 2009, Leskinen T et al. 2009). Only in rare cases, genetic predisposition strongly increases the risk of overweight and obesity (Farooqi IS et al. 2003), even at an early age.

2.2.3. Obesity and sedentary behaviour

Obesity, like sedentary behaviour, has been associated with an increased risk of non-communicable diseases. According to World Health Organization, overweight and obesity are leading risks for global deaths (3.4 million adults / year). Fourty-four % of type 2 diabetes, 23% of ischaemic heart disease and 7-41% of certain cancer burdens are attributable to overweight and obesity (WHO 2014). Especially intra-abdominal fat increases the risk of low-grade inflammation, which is associated with an increased risk of type 2 diabetes, metabolic syndrome, and cardiovascular diseases (Fain JN et al. 2004). Obesity has become a true global pandemic.

In experimental studies in humans, an increase in sedentary behaviour has resulted in reduced energy expenditure and an insulin resistance state (Stephens BR et al. 2011), and impaired insulin sensitivity and accumulation of abdominal fat (Olsen RH et al. 2008). In addition to genetic predisposition, at least three mechanisms have been suggested to explain the accumulation of body fat due to sedentary behaviour: First, very low muscular activity leading to positive energy balance (Hamilton MT et al. 2007). TV viewing is physically very passive, and therefore metabolism during TV viewing remains close to the resting metabolic rate (Hamilton MT et al. 2007, Katzmarzyk PT 2010, Ainsworth BE et al. 2011). This may be different from other sedentary behaviour types. Lack of non-exercise activity thermogenesis (low energy consuming activity, e.g. standing and fidgeting while sitting) has also been suspected to play a role in the accumulation of body fat (Levine JA et al. 1999, Levine JA et al. 2005, Levine JA 2007). Low energy consumption typically develops during prolonged TV viewing (Hamilton MT et al. 2007, Katzmarzyk PT 2010, Ainsworth BE et al.

2011). Secondly, higher energy intake associated with sedentary behaviour may confound or modify the association with adiposity (Pearson N et al. 2011). Sedentary behaviour may also replace physical exercise and time spent in other physical activities, which could result in reduced energy expenditure and increase in body weight (Hu FB et al. 2003).

With increased sedentary behaviour, reduced daily PA, and easier access to food, the energy surplus has increased, and obesity and non-communicable diseases have started to affect a larger part of the population (Lee IM et al. 2012). For children and adolescents sedentary lifestyle has become almost a standard, which may result in increased body weight and subsequent, more rapid development of cardiometabolic diseases than estimated earlier (Nobili V et al. 2009).

Due to the increased risks of obesity and non-communicable diseases and the concurrent decrease in PA and increase in sedentary time, more robust data is required on sedentary behaviour to understand its role in the development of the obesity pandemic.

2.3. Fatty liver

2.3.1. Definition and measurement

Fatty liver is defined as a disorder with increased hepatic triglyceride accumulation, i.e. liver fat content exceeds 5-10% by weight or as the percentage of fat-laden hepatocytes observed by light microscopy (Neuschwander-Tetri BA et al. 2003). This may be caused by excess alcohol intake, viral infection, other specific liver disease, or due to non-alcoholic fatty liver disease (NAFLD) with an unspecific origin.

In population studies the amount of fat in liver is best evaluated with hepatic ultrasound scan (Dasarathy S et al. 2009). Magnetic resonance imaging is more accurate in detecting smaller amounts of fat in the liver (Machado MV et al. 2013), but its use is limited due to higher cost. Liver biopsy, despite its highest accuracy, cannot be used in larger studies, and in relatively healthy populations, due to its invasive nature (Sumida Y et al. 2014). Liver function and the amount of hepatic fat can also be evaluated by measuring the concentration of enzymes primarily of hepatic origin, i.e. gamma-glutamyltransferase (GGT) or alanine aminotransferase, the rise of which are indicative of functional abnormalities and increased hepatic cell damage (Machado MV et al. 2013). Newer indicators of liver adiposity include e.g. Lipid accumulation product (LAP) combining fasting plasma triglyceride concentration and waist circumference. Fatty liver index (FLI) combining fasting plasma GGT concentration, fasting plasma triglyceride concentration, BMI and waist circumference data has been introduced to better and more reliably identify individuals with or in risk of developing fatty liver (Bedogni G et al. 2006, Bedogni G et al. 2010, Cuthbertson DJ et al. 2014).

2.3.2. Fatty liver and sedentary behaviour

NAFLD is estimated to affect 20-30% of adults, and the majority of obese individuals (Ryan MC et al. 2005, Sattar N et al. 2014, Suomela E et al. 2014). NAFLD prevalence has increased in parallel with the obesity pandemic (Demir M et al. 2015).

Fatty liver, like sedentary behaviour, is associated with increased risk of obesity (Clark JM et al. 2002, Wiechowska A et al. 2007), metabolic syndrome (Stefan N et al. 2008), insulin resistance (Adams LA et al. 2007), type 2 diabetes (Angulo P 2002), and cardiovascular diseases (Targher G et al. 2010). Fatty liver may result in liver inflammation, fibrosis, fat cell necrosis, and eventually even cirrhosis and liver cancer (Nobili V et al. 2009, Anderson EL et al. 2014). Liver fat accumulation in BMI-discordant monozygotic twins has been shown to be associated with lipid disturbances independent of genetics (Kaye SM et al. 2013), which emphasizes the role of lifestyle in its development.

In hyperphagic Otsuka Long-Evans Tokushima Fatty (OLETF) rats daily PA has been shown to prevent NAFLD by increasing hepatic mitochondrial content and function and by suppressing hepatic de novo lipogenesis (Rector RS et al. 2011). Physical inactivity together with obesity may be the cause of disruption in hepatic insulin signaling and subsequent NAFLD. In obese mice models of NAFLD, impaired hepatic insulin signaling under sedentary conditions markedly improves after an acute swimming bout (De Souza CT et al. 2010).

Data from physical inactivity studies show that decreased level of daily PA ($\leq$1 day/week vs. $\geq$3 days/week) is associated with increased incidence of NAFLD, and that women with lower PA have elevated liver enzyme concentration (Rudwill F et al. 2015). Enforced physical inactivity in healthy, normal-weight women increases hepatic markers of NAFLD (alanine/aspartate transaminase, cytokeratin, and angiopoietin-like protein3) with hypertriglyceridaemia suggesting alteration in hepatic metabolism independent of fat mass (Rudwill F et al. 2015).

Thus, current knowledge suggests that physical inactivity increases the risk of NAFLD, together or independently of obesity, but the exact mechanism remains unconfirmed. Despite a) the knowledge of the relationship between physical inactivity and fatty liver, b) the fact that fatty liver is an important factor involved in the development of cardiometabolic diseases, and c) despite the association seen between sedentary behaviour and increased risk of cardiometabolic diseases, the relationship of sedentary behaviour with fatty liver risk has not been studied.

3. AIMS OF THE STUDY

The main aim of this study was to investigate sedentary behaviour and health outcomes including obesity and fatty liver in Finnish adults. The specific aims of this study were:

1. To evaluate which type of sedentary behaviours are mostly responsible for the associations seen with high BMI and large waist circumference when controlling for a wide range of other risk factors for obesity (I).

2. To study the change in body weight and waist circumference in groups with different amount of sedentary time (TV viewing) in a longitudinal setting (II).

3. To study the direction of causal relationship between sedentary time (TV viewing) and weight increase in a longitudinal setting (II).

4. To study the association of sedentary time (TV viewing) with fatty liver by evaluating gamma-glutamyltransferase concentration, Fatty liver Index and liver ultrasound scan images (III).

4. SUBJECTS & METHODS

4.1. Subjects

All subjects of this study were from The Cardiovascular Risk in Young Finns Study, an ongoing multicenter follow-up study of atherosclerosis risk factors. The baseline cross-sectional survey was conducted in 1980, when 3,596 individuals aged 3–18 years participated. These participants were randomly chosen from the national registries of the five study districts. Since 1980, several follow-up studies have been conducted. The latest 30-year follow-up survey was performed in 2011 when 2,060 of the original participants (aged 33-50 years, of which 55 % were women) attended (Figure 1). To compare the subjects lost to follow-up and those staying in the study attrition analyses have been performed (Raitakari OT et al. 2008). Based on these evaluations, the study represents the general population very well. This, and the fact that data on various sedentary behaviour types, PA and a variety of factors having an impact on body weight and fat accumulation in liver have been collected during the follow-up of this study, makes it exceptionally useful for this kind of investigation that requires combination of patient demographics and background information together with various measurements and imaging.

Subject characteristics are presented in Table 1 below.

Table 1. Subject characteristics in different TV time groups in 2007.

TV time group (n)	Low (196)	Moderate (233)	High (84)	Increased (218)	Decreased (213)
Variable	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD
Gender (% female)	57.1	57.5	42.9	50.0	49.8
Age (years)	38.2 ± 4.8	38.5 ± 5.0	38.0 ± 5.1	39.8 ± 4.8	36.2 ± 4.6
MET (hrs/w)	16.3 ± 16.9	19.2 ± 19.2	17.5 ± 21.9	20.3 ± 23.2	20.7 ± 21.3
Occupation type (range 1-6)	3.5 ± 1.6	3.5 ± 1.6	3.9 ± 1.8	3.5 ± 1.5	3.5 ± 1.6
SES (range 1-3)	2.3 ± 0.9	2.1 ± 0.9	1.7 ± 0.8	2.1 ± 0.9	2.1 ± 0.9
Alcohol (doses/day)	0.5 ± 1.0	0.9 ± 1.0	1.9 ± 3.5	1.0 ± 1.5	0.9 ± 1.5
Smokers (%)	13.8	11.6	26.2	17.1	18.8
Energy intake/day (100 cal)	24.7 ± 6.4	23.4 ± 7.0	24.9 ± 10.1	24.4 ± 8.9	25.8 ± 9.8

n = Number of subjects in TV time group
Low = TV time ≤1 h/day in 2001, 2007 and 2011
Moderate = TV time >1h, but <3 h/day in 2001, 2007 and 2011
High = TV time ≥3 h/day in 2001, 2007 and 2011
Increased = TV time increased with ≥1 h/day between 2001 and 2011
Decreased = TV time decreased with ≥1 h/day between 2001 and 2011
hrs/w = hours per week
SES = Socioeconomic status
cal = Calories

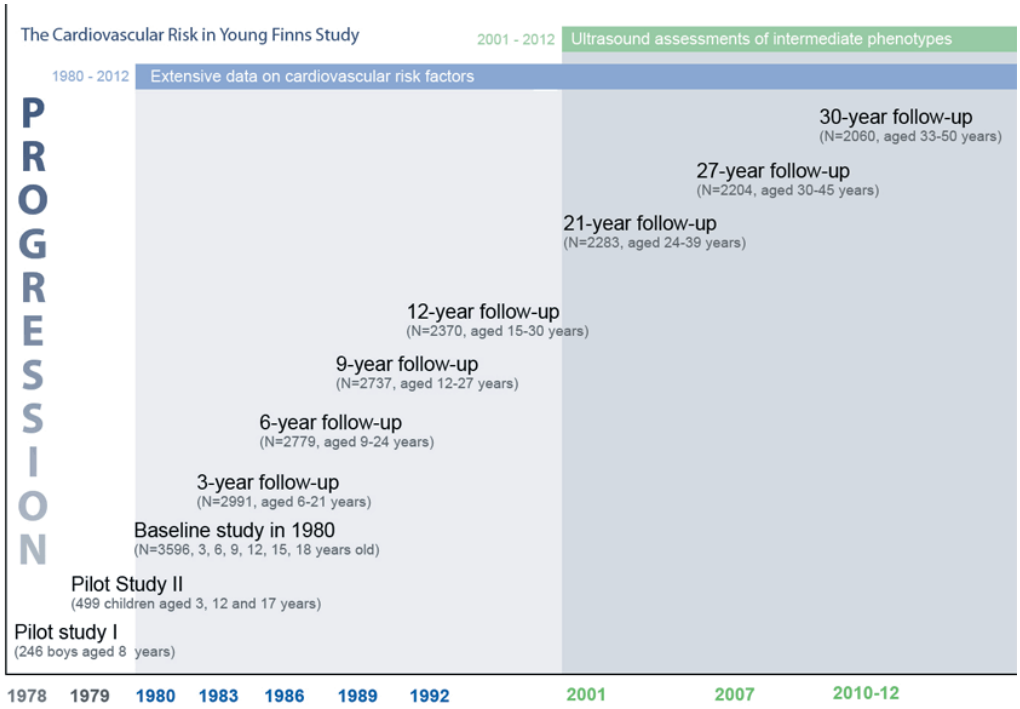

Figure 2. The progression of the Cardiovascular Risk in Young Finns Study.

In study I, the sample comprised 1,993 participants (1,084 women and 909 men) out of the total of 2204, who had a complete dataset including information on leisure-time sedentary behaviour subcategories (TV viewing, computer use, reading, listening to music, other relaxation), leisure-time PA, active commuting, BMI and waist circumference from the 27-year follow-up visit in 2007.

In studies II and III, a total of 1,387 participants (761 women and 626 men) who had data on TV viewing time, BMI and waist in 2001, 2007 and 2011, were included in the longitudinal BMI, waist circumference, GGT, and FLI evaluations.

2,040 subjects with liver ultrasound scan image from 2011 were included in the cross-sectional liver ultrasound scan study (III).

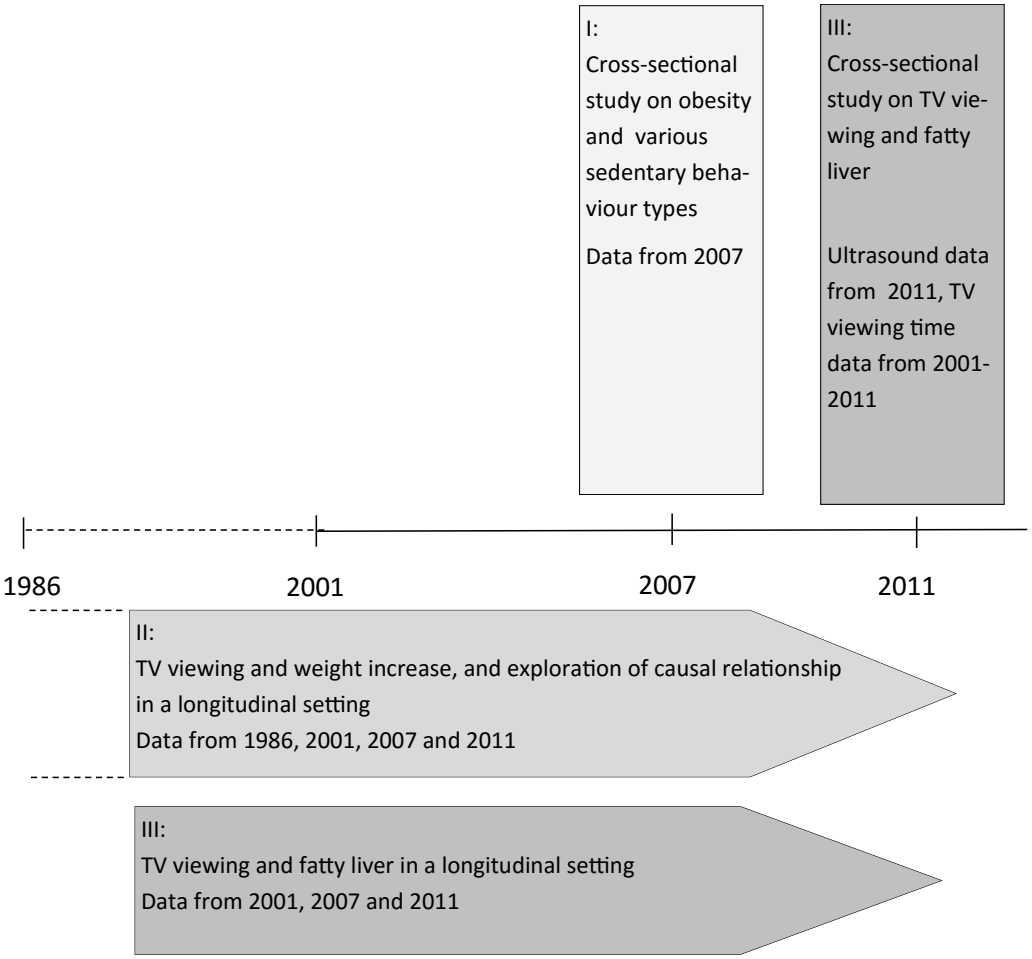

Figure 3. Overview of this study and its components.

4.2. Sedentary behaviour (I-III)

In studies I-III, self-administered questionnaire was used to collect data on leisure-time time spent 1) watching TV, 2) using computer, 3) reading, 4) listening to music/radio, and 5) in other type of relaxation. Total leisure-time sedentary time (h/day) was calculated based on time spent on all sedentary behaviour subcategories listed above (study I). In study I, also non-TV sedentary time (h/day) including time spent on all other sedentary behaviour but TV viewing was calculated. Screen time (h/day) was calculated as the sum of reported daily TV viewing time and computer hours. Work-related sedentary time and passive commuting were not calculated in the total sedentary time, but were considered in all analyses as they were reflected in the covariates adjusted for (occupational PA and MET index, respectively).

In study I the subjects were divided into four TV time groups ($\leq$1hour, 1-$\leq$2 hours, 2-3 hours, or $\geq$3 hours TV viewing a day), but in studies II and III into five TV viewing time

groups (≤1hour, 1-3 hours, or ≥3 hours TV viewing a day, or TV viewing time increased / decreased with at least 1 hour between 2001 and 2011). As TV viewing time in study I was the sedentary behaviour type mostly associated with negative health outcomes, it was used as a marker of sedentary time in studies II-III.

4.3. Body mass index and waist circumference (I-III)

In all studies body weight was measured with a digital scale in light clothing without shoes with the accuracy of 0.1 kg, and height with a wall-mounted stadiometer with the accuracy of 0.1 cm. BMI was calculated as kg/m^2. In studies I-III also waist circumference was measured with a non-elastic, but bendable, measuring tape in the end of expiration at the mid-axillary line between the iliac crest and the lowest rib. In study II, the BMI value in 1986 (at ages 9-24) was used to represent the BMI prior to the 10 years of study follow-up.

4.4. GGT and triglyceride concentration, FLI (III)

In study III, venous blood samples after an overnight fast were drawn and analysed using an AU 400 automatic analyser (Olympus, Hamburg, Germany). Serum GGT concentration was determined by a colorimetric method (GPO-PAP, Olympus System Reagent OSR6020), according to International Federation of Clinical Chemistry. The triglyceride concentration was determined by an enzymatic, colorimetric method (GPO-PAP, Olympus System Reagent, OSR6133 in 2001 and 2007, and OSR61118 in 2011). GGT concentrations from 2001 follow-up samples were measured in 2008. Triglyceride concentration values measured in 2007 and 2011 were corrected to reflect year 2001 levels. In study III, GGT and triglyceride concentrations together with BMI and waist circumference were used to calculate the FLI (Bedogni G et al. 2006)

4.5. Liver ultrasound (III)

In study III, the amount of hepatic fat in hepatic ultrasound scan images taken in 2011 was evaluated using a validated protocol based on an overall ultrasound image evaluation and calculation of four attenuation and textural indices (Edens MA et al. 2009). Sequoia 512 ultrasound mainframes (Acuson, Mountain View, CA, USA) and 4.0 MHz adult abdominal transducers were used. The diagnosis of fatty liver was primarily based on the overall visual evaluation of the images by a trained ultrasonographer, i.e. 1) normal or 2) fatty (18.3% of subjects with either mildly fatty or clearly fatty liver). Additionally, liver fat content was evaluated by combining four liver ultrasound parameters to create a continuous ultrasonographic Fatty Liver Index (uFLI, range 4-12) (Suomela E et al. 2014). The uFLI values >6 were defined as indicative of fatty liver (18.8% of subjects). The details of these evaluations are presented in Figure 4 below.

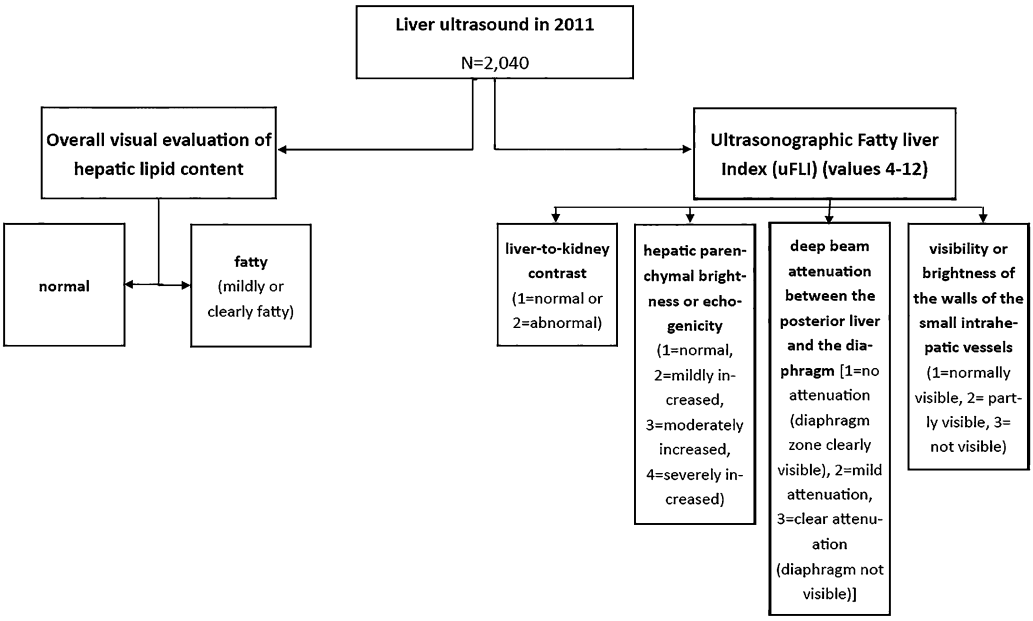

Figure 4. The two approaches taken in parallel to evaluate hepatic fat content with the liver ultrasound.

4.6. Possible confounders (I-III)

Various lifestyle and risk factors (in addition to age and sex) for the health outcomes investigated were considered during the study. They are described in more detail below.

4.6.1. Physical activity (I-III)

In all studies a self-administered questionnaire was used to assess leisure-time PA (I-III), active commuting (I, III), occupational PA (I-III), and household PA (I).

Leisure-time PA data was based on the reported frequency, duration, and intensity. The frequency was categorized as 1) not at all, 2) once a month, 3) once a week, 4) 2-3 times a week, 5) 4-6 times a week, or 6) daily. The average duration of a single bout of exercise was defined as 1) <20 minutes, 2) 20-40 minutes, 3) 40-60 minutes, or 4) >60 minutes. For PA intensity the categories were 1) not getting out of breath nor sweating, 2) getting out of breath and sweating slightly, or 3) getting out of breath and sweating heavily (Mansikkaniemi K et al. 2011). Active commuting evaluation was based on the reported commuting distance and active mode of commute (walking or bicycling).

In studies I and III, leisure-time PA and active commuting were combined to calculate a total PA index in MET hours per week. It was calculated by multiplying leisure-time PA intensity, frequency and duration, and adding the MET h/week from active commuting. The index has been validated against data collected with accelerometers and pedometers (Mansikkaniemi K et al. 2011). For the purpose of study I analyses, the participants were divided into three sex-specific PA index groups. In the low PA group, the PA index was <5

MET h/week both for men and women, and in the high PA group, the PA index was >22.8 MET h/week for men and >20.7 MET h/week for women.

In study II, a PA Index (PAI) was calculated based on leisure-time PA intensity, frequency and duration. A cumulative PAI index from PAIs in 2001, 2007, and 2011, was calculated to estimate the overall PA during the 10-year study period.

In addition, occupational PA was evaluated based on the reported work type, i.e. 1) light sedentary work 2) other sedentary work 3) physically light work, performed mainly standing, or including light activity 4) work including moderate PA 5) physically strenuous work, or 6) physically very strenuous work (Mälkiä E et al. 1988, Tammelin T et al. 2002). This question has previously been used in the population-based Mini-Finland Health Survey (Mälkiä E et al. 1988), and its test-retest reliability has been stated to be reasonably good (kappa coefficient 0.69) (Mälkiä E 1996).

In study I, also leisure-time spent in gardening and related housework (h/month) was taken into account. It was classified as light, moderate or strenuous PA.

4.6.2. Diet (I-III)

In all studies, data on energy intake, and quality of diet (diet score) were collected using a 131-item semi-quantitative food frequency questionnaire developed and validated by the Finnish National Institute for Health and Welfare by comparing the food frequency questionnaire to a 3-day food record (Paalanen L et al. 2006). The subjects were asked to report the daily frequency and serving size of selected foods and dishes during the previous 12 months. The questionnaire included also open questions to enable reporting of foods not listed in the FFQ. Daily specific food or food group consumption and nutrient intake were calculated using the latest version of the National Food Composition Database Fineli (Fineli 2007).

A food-based diet score was used as an indicator of healthy nutrition. With this score, each individual's adherence to nutrition recommendations (National Nutrition Council 2005, Lichtenstein AH et al. 2006, U.S. Department of Agriculture and U.S. Department of Health and Human Services 2011) was evaluated. This score has been constructed with a focus on cardiovascular disease risk. In study I, nine food groups in the score, which are unambiguously either to be preferred or avoided, were chosen and evaluated. Of these nine groups, whole grains, fish, fruits, vegetables and nuts were classified as favourable, whereas red and processed meats, sweets, sugar-sweetened beverages and fried potatoes as unfavourable foods. The consumption of each of these food groups was categorised in sex-specific quartiles and assigned ascending values (0, 1, 2 and 3) for favourable foods and descending values (3, 2, 1 and 0) for unfavourable foods. Thus, the quality of diet was evaluated as a score ranging from 1 to 27. For the purpose of study I, individual dietary items thought to represent the overall quality of diet, for example dietary carbohydrate content and calculated fibre-sucrose intake ratio, were selected for further analyses. All food items that correlated with TV viewing time in either sex, were selected as possible confounding factors in multivariable models.

4.6.3. Alcohol, smoking, sleep, and socioeconomic status (I-III)

A standardized questionnaire was used to collect data on alcohol consumption, smoking, sleep duration, and socioeconomic status. Daily alcohol consumption as standard drinks (12g pure ethanol) was calculated from self-reported doses (0.33 L of beer or cider, 0.12 L of wine, and 0.04 L of hard liquor) per week divided by seven. Smoking status was based on self-reporting of current smoking or non-smoking (studies I-III). Sleep duration was based on self-reported, usual hours of sleep per night (range from $\leq$5 hours to $\geq$10 hours, scaling every 30 min).

Socioeconomic status was determined based on self-reported occupation categorized as 1) manual, 2) lower, non-manual or 3) upper, non-manual.

4.6.4. Genetic variants (I)

In study I, data on 31 single nucleotide polymorphisms (SNPs) that have been shown to be associated with increased risk of high body weight (Speliotes EK et al. 2010) were used to create a genetic obesity risk score calculated as a weighted scale variable of risk alleles in these 31 SNPs (Juonala M et al. 2011). These variants were derived from the genome-wide analysis performed with Illumina Bead Chip (Human 670K, Welcome Trust Sanger Institute, UK).

5. DATA ANALYSIS

5.1. Cross-sectional analyses (I, III)

In the cross-sectional study I, univariate models (Spearman's correlation coefficients) were calculated by sex to identify the sedentary behaviour(s) and PA type(s) with the strongest associations with high BMI and large waist circumference as well as risk factors for obesity. Sex differences for study variables were analysed with the non-parametric Wilcoxon two-sample test.

In study I, multivariate-adjusted analyses were performed to study the associations of TV viewing time, total sedentary time, and non-TV sedentary time with high body weight. Linearity between covariates and BMI / waist circumference was evaluated with plot charts, and covariates with significant non-linear association were included in the multivariate models as their quadratic forms. Four-step multivariate analyses were made to test the magnitude of the influence by various covariates as follows: 1) adjusting for obesity gene variants and other lifestyle factors except diet, 2) adjusting additionally for energy intake and diet score, 3) adjusting additionally for all individual dietary items associated with TV viewing.

In addition in study I, to evaluate how much TV viewing time and non-TV sedentary time increased the risk of obesity, age- and sex- and other obesity covariate adjusted relative risks for obesity were calculated using generalised linear modelling. The obesity outcome variable was defined by sex-specific waist circumference cut-off points (>88 cm in women and >102 cm in men). The other covariates adjusted for in the analyses were genetic obesity risk score, energy intake, diet score and specific dietary items associated with TV viewing, and in addition, alcohol consumption, PA, smoking, sleep duration and socioeconomic status. Similar analyses were made for non-TV sedentary time. In study I, data was analysed with all subjects together and by sex.

As the last step in study I, age- and sex-adjusted waist circumference in 2007 was studied according to TV viewing and non-TV sedentary time within the different PA index groups. In study II, the relative risks of obesity (cut-off defined as BMI $\geq$30 kg/m^2) considering the 10-year TV viewing time were calculated for all study subjects together using generalised linear modelling. These analyses were adjusted for age, sex, leisure-time PA, energy intake, and smoking in 2007. In a similar manner, in study III, generalised linear modelling was used to calculate the relative risk of TV viewing time for ultrasonograpically detected fatty liver for all study subjects. The covariates adjusted for were age, sex, leisure-time and occupational PA, energy intake, diet score, alcohol use, sleep duration, socioeconomic status, smoking, and BMI in 2007. Similar analyses were performed for men and women separately.

5.2. Longitudinal analyses (II, III)

In study II, two different methods were used to study the causal relationship of TV viewing time with weight gain between 2001 and 2011. The first evaluation was done according to classical temporality criterion (Hill AB 1965), but the other analysis applied the recently

introduced, distribution-based pairwise causality estimates, so called Linear, Non-Gaussian, Acyclic Model where the direction of causality can be determined even from cross-sectional data (Shimizu S et al. 2006). Two different pairwise measures of causality, DirectLiNGAM- and entropy-based (Shimizu S et al. 2011, Hyvärinen A et al. 2013), were applied. These measures are based on the assumptions that a) either obesity causes TV time or TV time causes obesity, b) the causal association is linear, c) independent residual terms are non-Gaussian (distributed according to some other than the Normal distribution), and that d) there are no (strongly/fully) confounding variables.

Weight and waist circumference changes (study II), and GGT concentration and FLI changes (study III) in TV viewing time groups during the 10-year study period (2001-2007-2011) were evaluated by calculating the mean BMIs, waist circumferences, GGTs and FLIs, and differences between the TV viewing time groups with linear regression, multiple comparison corrected (Tukey-Kramer) test. In addition, the magnitude of the mean BMI and waist circumference (study II), and GGT concentration and FLI changes (study III) in all TV time groups during the 10-year follow-up we evaluated. T-test was used to compare the differences between the extreme TV viewing time groups, i.e. those with constantly high and constantly low TV viewing time.

In study III, the specificity and sensitivity of the FLI and GGT concentration were estimated by calculating their Areas Under Curves (AUCs) and comparing them to the direct liver ultrasound scan fatty liver diagnosis and uFLI. In this study the AUC for FLI vs. overall visual evaluation of liver ultrasound images was 0.86 (0.84-0.88), and vs. uFLI 0.83 (0.81-0.85). The respective AUCs for GGT concentration were 0.81 (0.79-0.83), and 0.78 (0.75-0.80). According to these, the different methods correlate relatively well in estimating fatty liver.

In studies II-III, data were analysed with all subjects combined, but due to sex-by-TV interaction at least at one time point during the study (in 2001, 2007 or 2011), also sex-stratified BMI and waist circumference (study II), and GGT concentration, FLI, and uFLI analyses (study III) were performed.

Grouping of subjects to the five TV viewing time groups in studies II and III excluded participants (428 and 423, respectively). Therefore, attrition analyses comparing the excluded and included subjects were performed using non-parametric Wilcoxon 2-sample test. There were no differences in age, BMI, waist circumference, or TV time in 2001, but the excluded subjects were more often women. According to this analysis the subjects remaining in the TV viewing time groups are representative of the whole study population.

All statistical analyses were done with SAS version 9.2 (studies I and II) or 9.4 (study III). The statistical significance was inferred at a 2-tailed probability value <0.05.

6. RESULTS

6.1. Obesity (studies I, II)

High sedentary time, especially TV viewing, was related to higher body weight and increased risk of obesity (studies I-II). In the cross-sectional setting (study I) one additional TV viewing hour was associated with a mean 1.8 (SD ±0.4 cm) cm larger waist circumference in women and mean 2.0 cm (SD ±0.4 cm) in men. High TV viewing time (≥3h/day) was associated with higher consumption of sausage, beer and soft drinks, and lower consumption of oat and barley, fish, and fruits and berries suggesting that the obesogenic effect of TV viewing may be mediated partly via dietary factors. Similar associations with diet were not seen with computer use and reading (study I). Nevertheless, in this study, the associations of TV viewing time with BMI or waist circumference were independent from leisure-time and occupational PA, energy intake, diet score, alcohol, smoking, socioeconomic status, sleep duration, age, sex, and genetic predisposition for high BMI. These factors only partially attenuated the association of TV viewing and obesity (studies I-II).

According to study II, the increase in BMI and waist circumference during the 10-year study was more than 2-fold in individuals watching TV constantly for 3 hours or more in comparison to those watching TV constantly for 1 hour or less a day (Table 2).

Table 2. Mean waist circumference and BMI in 1986, 2001 and 2011, and change in waist and BMI from 2001 to 2007, and from 2001 to 2011 in different TV time groups. Tukey-Kramer corrected pairwise TV group comparisons of BMI and waist changes in constantly high and constantly low TV time groups between 2001 and 2011.

TV time between 2001 and 2011 (n)	**1986**	**2001**		**2011**		**Change from 2001 to 2007***		**Change from 2001 to 2011***	
	BMI (kg/m^2)	**Waist** (cm)	**BMI** (kg/m^2)	**Waist** (cm)	**BMI** (kg/m^2)	**Waist** (cm)	**BMI** (kg/m^2)	**Waist** (cm)	**BMI** (kg/m^2)
Low (200)	20.2	82.7	24.3	89.4	25.9	3.0	0.5	5.0	0.8
Moderate (238)	20.4	85.4	25.4[1]	92.5[1]	26.7[1]	5.5[1]	1.2[1]	8.4[1]	1.7[1]
High (84)	20.6	86.9[1]	26.0[1]	94.9[1]	27.5[1]	6.7[1]	1.7[1]	10.9[1]	2.5[1]
Increased (221)	21.2	85.0	25.2	92.7[1]	26.9[1]	5.0[1]	1.2[1]	8.3[1]	1.8[1]
Decreased (216)	19.4[4]	84.0	25.0	91.7[1,3]	26.4[3]	4.8	0.9[3]	7.4[1,3]	1.3[3]
All (1387)	20.3	83.9	24.9	91.6	26.5	4.6	1.0	7.7	1.6

n = All available observations for the variable in question
Waist = Waist circumference
BMI = Body mass index
Low = TV time constantly ≤1 h/day between 2001 and 2011
Moderate = TV time constantly >1h, but <3 h/day between 2001 and 2011
High = TV time constantly ≥3 h/day between 2001 and 2011
Increased = TV time increased with ≥1 h/day between 2001 and 2011
Decreased = TV time decreased with ≥1 h/day between 2001 and 2011
*= adjusted by sex, age, physical activity, energy intake, smoking, and waist or BMI in 2001
Tukey-Kramer adjusted pairwise comparisons:
1=statistically significant difference with Low group ($p<0.05$)
3=statistically significant difference with High group ($p<0.05$)
4=statistically significant difference with Increase group ($p<0.05$)

The relative risk for high BMI (BMI≥30kg/m^2) was increased both in the constantly moderate (1-3 h/day) and in the constantly high (≥3h/day) TV time group when compared to the constantly low TV time (≤1h/day) group. The BMI and waist increases were independent from leisure-time and occupational PA, energy intake, diet score, alcohol, smoking, socioeconomic status, sleep, age and sex (Table 3).

Table 3. Relative risk of obesity (BMI ≥30 kg/m^2) associated with TV viewing time. Analyses adjusted with age, sex, physical activity, energy intake, and smoking.

TV viewing time between 2001 and 2011	Relative Risk in comparison to reference (95% CI; p-value)
Low (n=200)	1.00 (reference)
Moderate (n=238)	2.1 (1.2-3.5; 0.007)
High (n=84)	3.1 (1.7-5.7; 0.0002)
Increased (n=221)	2.0 (1.2-3.4; 0.01)
Decreased (n=216)	1.9 (1.1-3.4; 0.02)

BMI = Body mass index
n = All available observations for the variable in question
Low = TV viewing time constantly ≤1 h/day between 2001 and 2011
Moderate = TV viewing time constantly >1h, but <3 h/day between 2001 and 2011
High = TV viewing time constantly ≥3 h/day between 2001 and 2011
Increased = TV viewing time increased with ≥1 h/day between 2001 and 2011
Decreased = TV viewing time decreased with ≥1 h/day between 2001 and 2011

6.2. Causal relationship (study II)

According to the causality assessment in study II, sedentary behaviour (TV viewing) is causative to weight gain, and not the other way round, regardless of whether the causal association is explored using the classical temporality criterion or more recently introduced distribution-based pairwise causality estimates (DirectLiNGAM- or entropy-based). TV time correlated positively both with waist circumference and BMI in 2001, 2007, and 2011 (Pearson's r≥0.078 in all; Table 4). Furthermore, TV viewing time in 2001 predicted subsequent increase of both BMI and waist circumference, but neither BMI nor waist at baseline predicted changes in TV viewing time. Also the kernel-based measure of causality indicated that TV viewing time was causally antecedent for BMI and waist increase, although the measure did not reach statistical significance in all pairwise comparisons (Table 4). No suggestion of a reverse causal relationship was seen in the pairwise analyses. This is an important new finding, as by increasing body weight high sedentary time could increase the risk of non-communicable diseases associated with obesity.

Table 4. Correlations and Pairwise Causality Statistics between the study variables (TV time, waist circumference and BMI).

Comparison	r (95% CI)	T_{kernel} (95% CI)	$T_{entropy}$ (95% CI)
Cross-sectional evaluation			
TV time vs. Waist, 2001	**0.126 (0.085, 0.167)**	**0.015 (0.000, 0.032)**	0.001 (-0.006, 0.007)
TV time vs. Waist, 2007	**0.187 (0.146, 0.227)**	**0.175 (0.097, 0.276)**	-0.011 (-0.027, 0.001)
TV time vs. Waist, 2011	**0.203 (0.160, 0.245)**	0.011 (-0.009, 0.037)	-0.014 (-0.052, 0.022)
TV time vs. BMI, 2001	**0.116 (0.075, 0.156)**	0.014 (-0.006, 0.030)	-0.001 (-0.008, 0.006)
TV time vs. BMI, 2007	**0.185 (0.144, 0.225)**	**0.164 (0.091, 0.260)**	-0.012 (-0.029, 0.003)
TV time vs. BMI, 2011	**0.170 (0.127, 0.213)**	0.005 (-0.018, 0.031)	-0.020 (-0.0512, 0.005)
Longitudinal evaluation			
TV time vs. Δ_{6y}Waist	**0.101 (0.055, 0.148)**	**0.018 (0.004, 0.039)**	-0.001 (-0.007, 0.006)
Waist vs. Δ_{6y}TV time	0.011 (-0.035, 0.057)	-0.001 (-0.014, 0.001)	0.000 (-0.002, 0.002)
TV time vs. Δ_{10y} Waist	**0.110 (0.062, 0.157)**	**0.023 (0.008, 0.043)**	0.000 (-0.005, 0.008)
Waist vs. Δ_{10y}TV time	0.030 (-0.019, 0.078)	-0.001 (-0.011, 0.001)	-0.002 (-0.017, 0.002)
TV time vs. Δ_{6y}BMI	**0.078 (0.032, 0.124)**	**0.012 (0.001, 0.030)**	0.000 (-0.007, 0.007)
BMI vs. Δ_{6y}TV time	0.020 (-0.026, 0.066)	-0.001 (-0.017, 0.001)	0.000 (-0.002, 0.003)
TV time vs. Δ_{10y}BMI	**0.085 (0.038, 0.133)**	**0.014 (0.001, 0.035)**	0.001 (-0.005, 0.009)
BMI vs. Δ_{10y}TV time	0.018 (-0.031, 0.066)	0.000 (-0.006, 0.002)	0.000 (-0.011, 0.003)

Positive value of T_{kernel} or $T_{entropy}$ suggests that the first-mentioned variable in each comparison is causally antecedent of the secondly mentioned, whereas a negative value implies the opposite. Parentheses give 95% bootstrap-percentile confidence intervals of estimates, except for ordinary correlation for which standard asymptotic theory was used. Statistically significant comparisons are highlighted with bold font.
TV time = TV viewing time
Δ_{6y} = change over six years (from 2001 to 2007)
Δ_{10y} = change over ten years (from 2001 to 2011)
Waist = Waist circumference
BMI = Body mass index
r = Correlation coefficient
T_{kernel} = DirectLiNGAM- and Kernel-based measure of pairwise causality
$T_{entropy}$ = Approximate-entropy and asymptotic-likelihood –based measure of pairwise causality

6.3. Fatty liver (study III)

A direct association with constantly high sedentary time (TV viewing ≥3h/day) and fatty liver was seen regardless of the indicator of fatty liver used (serum GGT concentration, FLI, or hepatic ultrasound scan images). The association was seen both in the longitudinal and cross-sectional settings, and it remained despite adjustment for cofactors like PA, diet and alcohol. Serum GGT concentration and FLI increases during the 10-year follow-up were over 3-fold in subjects watching TV constantly for 3 hours or more when compared to those watching TV for 1 hour or less a day (Table 5).

Table 5. Mean increase in GGT and FLI during the 10-year follow-up in all TV time groups and by sex, and the difference between the constantly high and constantly low TV time groups. Analyses are adjusted for age and sex, baseline FLI, leisure-time and occupational PA, energy intake, diet composition, alcohol use, sleep duration, socioeconomic status, and smoking. BMI is included in the FLI as per definition.

	Low (SD)	**Moderate** (SD)	**High** (SD)	**Increased** (SD)	**Decreased** (SD)	**Difference (%) High vs. Low**
GGT (U/l)	**n=196**	**n=233**	**n=84**	**n=218**	**n=213**	
All	6.2 (18.5)	5.7 (26.8)	23.2 (62.7)	12.6 (34.7)	8.6 (29.1)	+374 *
Women	5.7 (16.7)	5.6 (33.3)	18.0 (50.0)	5.2 (14.1)	8.5 (32.7)	+316 *
Men	6.8 (20.8)	5.9 (13.9)	27.0 (71.0)	19.9 (46.0)	8.7 (25.1)	+397 *
FLI (range 0-7)						
All	1.3 (4.9)	1.3 (5.7)	5.0 (12.6)	3.3 (9.0)	2.2 (8.6)	+385 *
Women	1.1 (4.7)	1.1 (6.0)	5.4 (13.9)	2.1 (7.6)	2.1 (8.4)	+491 *
Men	1.7 (5.1)	1.6 (5.2)	4.6 (11.7)	4.5 (10.1)	2.3 (8.8)	+271 *

SD = standard deviation
GGT = serum gamma-glutamyltrasferase concentration
n = Number of subjects in group
FLI = fatty liver index
Low = TV viewing time constantly ≤1h/day between 2001 and 2011
Moderate = TV viewing time constantly 1-3h/day between 2001 and 2011
High = TV viewing time constantly ≥3h/day between 2001 and 2011
Increased = TV viewing time increased with ≥1h between 2001 and 2011
Decreased = TV viewing time decreased with ≥1h between 2001 and 2011
* = Difference in increase between constantly high (≥3h/day) and constantly low (≤1h/day) TV time groups ($p<0.0001$ in all)

According to the hepatic ultrasound scan images, the relative risk of fatty liver was 2.3-fold (95%CI 1.22-4.48) in subjects spending constantly 3 hours or more in front of TV in comparison to those who watched TV for only 1 hour or less a day during the 10-year follow-up despite adjustment for other covariates known to de-/increase fatty liver risk (Table 6).

Table 6. Relative risks (RRs) and 95% Confidence Intervals (95%CI) for ultrasound diagnosis of fatty liver in all TV time groups. Generalised linear modelling is adjusted for age and sex, leisure-time and occupational PA, energy intake, diet score, alcohol use, sleep duration, socioeconomic status, and smoking. Two analyses were done, one with and the other without BMI.

TV group	**All** (n=1084)		**Women** (n=586)		**Men** (n=498)	
Without BMI	**RR**	**95%CI**	**RR**	**95%CI**	**RR**	**95%CI**
Low TV time	1.00		1.00		1.00	
Moderate TV time	1.17	0.65-2.11	1.15	0.37-3.53	1.13	0.56-2.26
High TV time	***2.34***	***1.22-4.48***	2.15	0.56-8.23	***2.44***	***1.16-5.16***
Increased TV time	1.41	0.80-2.48	1.31	0.43-4.01	1.33	0.68-2.59
Decreased TV time	1.38	0.76-2.51	1.74	0.53-3.85	1.19	0.59-2.41
With BMI	**RR**	**95%CI**	**RR**	**95%CI**	**RR**	**95%CI**
Low TV time	1.00		1.00		1.00	
Moderate TV time	1.03	0.57-1.87	0.75	0.24-2.35	1.07	0.53-2.15
High TV time	1.75	0.91-3.38	0.82	0.20-3.33	***2.19***	***1.03-4.66***
Increased TV time	1.11	0.62-1.96	0.80	0.24-2.61	1.12	0.57-2.18
Decreased TV time	1.12	0.61-2.04	1.40	0.44-4.44	1.01	0.50-2.05

Low TV time = TV viewing time constantly ≤1h/day between 2001 and 2011
Moderate TV time = TV viewing time constantly 1-3h/day between 2001 and 2011
High TV time = TV viewing time constantly ≥3h/day between 2001 and 2011
Increased TV time = TV viewing time increased with ≥1h between 2001 and 2011
Decreased TV time = TV viewing time decreased with ≥1h between 2001 and 2011
Based on the obesity and fatty liver analyses, sedentary behaviour is independently associated with fatty liver. This association is most probably mediated by increase in body weight.

7. DISCUSSION

1.1. Summary of the main findings

1. TV viewing is the sedentary behaviour type mostly responsible for the association between sedentary time and high BMI and large waist circumference despite leisure-time and occupational PA, energy intake, quality of diet, alcohol, smoking, socioeconomic status, sleep, age, sex, and genetic predisposition for high BMI (study I).

2. Long-term sedentary behaviour (TV viewing time) is associated with larger increases in BMI and waist circumference in a longitudinal setting despite leisure-time and occupational PA, energy intake, quality of diet, alcohol, smoking, socioeconomic status, sleep, age, and sex (study II).

3. Sedentary behaviour (TV viewing) is causally antecedent to weight gain and not the other way around (study II).

4. TV viewing time is associated with increased risk of fatty liver independently from leisure-time and occupational PA, energy intake, quality of diet, alcohol, smoking, socioeconomic status, sleep, age and sex (study III). This finding was repeated using various outcomes (GGT concentration or FLI change in a longitudinal, and liver ultrasound scan images in a cross-sectional setting). The association of sedentary time with fatty liver is most probably mediated by weight increase.

Of the cofactors adjusted for, occupational PA, sleep duration, diet score (in all studies), and 31 gene variants increasing the risk for high BMI (in study I), were evaluated in a sedentary behaviour study for the first time.

7.1. The role of TV viewing

Based on this study, TV viewing is the sedentary behaviour type mostly responsible for the associations with obesity and fatty liver. This could be due to the fact that it is truly more hazardous to health than other types of sitting, e.g. due to its abundance, passive nature and the prolonged bouts of sedentary time that it may cause. On the other hand, it is a measure that is more easily and reliably recallable, and more accurately documented, than other sedentary time, when using subjective data collection methods (Clark BK et al. 2009, Clemes SA et al. 2012). Therefore, it may simply be a reliable surrogate of all sedentary time that might have similar associations. As some sedentary behaviour types may also be done alongside with other activities (e.g. listening to music during household work or PA), they may not fully reflect sedentary time and have similar associations as TV viewing time. High TV viewing time may also be linked to other factors, e.g. socioeconomic status and other unhealthy behaviours, which may have an additional negative impact on health.

7.2. Possible confounders

7.2.1. Diet

The findings from this study are biologically plausible. They confirm and add to the results from earlier sedentary behaviour studies, especially the importance of TV viewing time and the independent association of sedentary time with obesity. Nevertheless, sedentary behaviour, especially TV viewing, may be associated with other unhealthy behaviours. Such association has been shown in children's dietary habits while watching TV (Pearson N et al. 2011). Dietary habits can also be influenced in various ways, i.e. prior television experience predicts unhealthy food preferences and diet in early adulthood, and perceived taste has the most direct relationship to both healthy and unhealthy diets. Both television experience and parenting factors independently influence these preferences and diet (Harris JL et al. 2013).

This study indicated that individuals with higher TV viewing time consumed more frequent unhealthy food items, but that did not dilute the association seen between high TV viewing time and obesity. Behavioural or psychological factors, or the physical or social environment, that may also play a role, were not evaluated in this study. The different kind of correlation of diet with different types of sedentary behaviour warrant further investigations.

7.2.2. Genetic predisposition

Genetic predisposition may play a role in promoting sedentary behaviour: high BMI may result in more time spent sedentary (Ekelund et al. 2008), or genes may either prevent a physically active or promote a physically inactive lifestyle (Stubbe JH et al. 2006, de Vilhena e Santos DM et al. 2012). Also the experience of PA, or physical inactivity, may vary depending on genes (de Geus EJC et al. 2008). As genes may also define the sensitivity of target organs to any given risk, or define their metabolic capacity or function, they may either increase or decrease the magnitude of the effect of PA or physical inactivity (Bouchard C et al. 2012).

In this study, the 31 genetic variants that increase the risk for high BMI were associated with higher body weight, but they did not dilute the association between sedentary behaviour (TV viewing time) and increased body weight. This underlines the independent nature of sedentary time. Epigenetic changes caused by the way we live (Horsburgh S et al. 2015) could not be evaluated as part of this study, although sedentary lifestyle, similarly with other unhealthy behaviours, may potentially induce epigenetic changes, e.g. pro- and anti-inflammatory processes due to PA or lack of it.

7.3. Methodological considerations

7.3.1. Strengths

The 10-year, longitudinal dataset adds significantly to the value of this study. The strength of this study is also the relatively large study sample representative of the general population, and the fact that a large number of important risks and covariates could be considered in

all analyses. Some of these factors (occupational PA, sleep duration, diet score, and 31 gene variants increasing the risk for high BMI) were evaluated in a sedentary study for the first time. Also the use of various outcomes and different types of new analyses in one study, e.g. in the causality exploration (II) and fatty liver study (III) further strengthen this study.

7.3.2. Limitations

Subjective reporting of sedentary time, PA, and nutrition are limitations, which may either under- (diet, alcohol consumption, sedentary time) or overestimate (PA) the reported amount, especially in some subject groups, e.g. in overweight and obese (Paalanen L et al. 2006), and heavy drinkers (Feunekes GI et al. 1999), but as the purpose of this study was not to look for exact numbers for these variables per se, but overall trends on a population level, the bias is limited. Nevertheless, possible errors or inaccuracies in the subjective reporting of confounders used for adjustment purposes may reduce their impact and modify the associations seen between sedentary time and the studied health outcomes. Based on the internal validity of the study data alcohol consumption was strongly associated with HDL-cholesterol and gamma-GT levels (Juonala M et al. 2009), which speaks for relatively reliable data. The amount of alcohol consumption was ascertained during the past week prior the study, and it has been previously shown that the reported levels of alcohol intake are not related to the length of reference period (Feunekes GI et al. 1999), which adds further to the reliability of the alcohol consumption data.

Of various sedentary behaviour types, self-reported TV viewing time is relatively reliable (Clark BK et al. 2009), which decreases the significance of this limitation. On the other hand, with objective PA measurement alone, different types of sedentary behaviour could not have been distinguished the way they were in the current setting. Sedentary time during the working day or sitting while commuting per se were not evaluated in this study, but information on the occupation type (and work related PA) and commuting as part of the PA index were evaluated as covariates in the analyses performed.

Although data on energy intake and diet quality was available in this study, eating while watching TV could not be evaluated.

This study could not take into consideration the duration of sedentary bouts or breaks between them, that may reduce the health risks associated with high sedentary time (Healy GN et al. 2008, Latouche C et al. 2013). Also regular PA and good cardiorespiratory fitness help maintain normal body weight, and reduce the associated disease risks and mortality (Rauramaa et al. 1995, Barry VW et al. 2014). However, the impact of fitness on the studied health outcomes (Johnson NA et al. 2010, Barry VW et al. 2014, Loprinzi P et al. 2014) could not be evaluated in this study.

7.4. Implications for future studies

7.4.1. Metabolic pathways and effects on target organs

For both sedentary behaviour and PA studies one main goal is to identify the physiological changes caused by changes (increase or decrease) in PA or sedentary behaviour. There is

some preclinical evidence that physical inactivity may have direct effects on our metabolism, e.g. insulin resistance (Sarvas JL et al. 2015) and fatty liver (De Souza GT et a. 2010). Similar findings have been seen in sedentary behaviour intervention studies in humans (Saunders TJ et al. 2012). Nevertheless, the direct and indirect role of sedentary behaviour is still poorly understood, and discussion continues on whether the associations seen are due to physical inactivity or lack of PA. Some studies have even shown that even individuals spending most of their time in an upright position, i.e. standing, may have a lower risk of premature death than those spending most of their time sitting. (Katzmarzyk PT 2014). Therefore, the metabolic pathways involved around PA, physical inactivity and sedentary behaviour need to be investigated further to fully understand and distinguish between the direct and indirect effects of sitting on health, and target organs like fat, liver, cardiovascular system and even brain.

7.4.2. Intervention studies

High-quality intervention studies are needed to understand the effects of sedentary behaviour on health and the mechanistic pathways, but a healthy body can for a while counterbalance many changes from happening. This limits what one can detect during a shorter follow-up after an intervention. Various types of interventions in different settings, with different approaches, in different target groups, and with good control for confounders, are needed.

7.4.3. Data collection

Objective data collection is important, but even with the most accurate objective data collection methods it is not possible to capture the type of sedentary behaviour and the context around a bout of sitting. Use of advanced technology needs to be evaluated (e.g. by prompted questions after a longer bout of sitting) to improve data quality, but some level of subjective input may be needed.

7.4.4. Causal relationship

This study was the first to explore the causal relationship between sedentary behaviour and gain in body weight using different methods (classical temporality criterion and novel pairwise causality estimates). The results from the traditional causality explorations were in line with the pairwise causality estimates, but only kernel- and DirectLiNGAM-based measure provided useful information, whereas the approximate-entropy approach to asymptotic likelihood ratio did not reach statistical significance. This was most probably due to the presence of partially confounding unobserved factors, as kernel- and Direct Linear, Non-Gaussian, Acyclic model, that base their recommendation on simulations on partial confounding excelled over the approximate-entropy approach.

The principles of causality assessment have been presented by Bradford Hill earlier (Hill AB 1965), but new ways to explore causal relationships need to be developed and evaluated to efficiently obtain missing pieces of evidence from differently designed studies, and to confirm the novel finding from this study. Only by critically and innovatively combining

existing and new data, a true picture around sedentary behaviour and its impact on health can be built. Partial confounding effects may be of interest for future studies aiming to understand the differences between the kernel-based and entropy-approximation methods.

7.4.5. Genetics

The degree of PA and sedentary behaviour can, to certain extent, be coded in our genes, and this also needs to be studied further. Identification of gene variants encouraging us to be more or less active or those that make individuals react adversely to PA or sedentary behaviour is essential. Also, a better understanding of epigenetics, i.e. how and to what extent the behaviours and lifestyle modify the function of genes is important to fully understand the complex connections between sedentary behaviour, obesity and fatty liver.

7.4.6. Making behaviour change

To reduce sedentary behaviour, methods and interventions distinct from those traditionally used to promote PA are needed. As with any intervention, the means and tools to change behaviour vary depending on the context and the target population. To make permanent change in sedentary behaviour, one needs to understand the complex psychology around sedentary lifestyle, and factors behind the choices we make to "make the sofa less tempting and the behaviour change worth the effort". To achieve this, a better understanding of the correlates and characteristics of target populations, and individuals' needs, i.e. use of social marketing principles, are needed. In order to achieve the ultimate goal, i.e. permanent change on the individual and population level in a real-life setting, a wider scientific and societal collaboration is needed to be able to consider relevant behavioural, psychological and social aspects in future studies.

8. CONCLUSIONS AND IMPLICATIONS

- Based on this study, TV viewing is the sedentary behaviour mostly responsible for the associations seen with high BMI and large waist circumference, despite adjustment for a wide range of other factors having an impact on obesity, e.g. PA and diet. An independent, increased risk of obesity was seen in more sedentary individuals (with higher TV viewing time) also in a longitudinal setting. As obesity is such an important risk for health, and TV viewing time is a modifiable behaviour, ways to reduce it in a real-life setting need to be evaluated. Further investigations are also needed to confirm the truly independent nature of sedentary behaviour, and TV viewing time, on weight gain.

- Sedentary behaviour (TV viewing) is causal to weight increase, and not the other way around. This finding emphasizes the need to find efficient ways and methods to reduce TV viewing time and prolonged, passive sitting bouts associated with it. After all, a significant amount of sedentary time is nowadays spent in front of TV. In the future, the change in TV viewing habits, e.g. use of mobile technology, may require setting up slightly different types of studies to evaluate their impact. Additional studies are needed to investigate the causal relationship with obesity further, and to study the causal relationship with non-communicable diseases in various types of study settings.

- Sedentary behaviour (TV viewing) is associated with fatty liver despite of other factors having an impact on fatty liver risk. This association was seen with all methods (GGT concentration, FLI or liver ultrasound) used. This is the first study to detect such an organ-level association in a longitudinal setting, and emphasizes that sedentary behaviour may be one of the factors behind the obesity pandemic and increased prevalence of fatty liver, conditions that are both associated with higher risk of non-communicable diseases. Further studies to investigate the mechanistic pathways and possible direct effects of sedentary behaviour on liver, cardiovascular system and brain, but also on muscle and fat, are needed.

To conclude, leading and active lifestyle without too much and too long sedentary bouts may be one low-threshold way to reduce the risk of obesity and fatty liver, and potentially reduce the non-communicable disease risks associated with obesity.

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Opponent

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