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JYVÄSKYLÄN YLIOPISTO

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ABSTRACT

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English Summary
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Weight gain through midlife is common in both men and women, increasing the risk for earlier onset of functional limitations and disability later in life. Previous studies have suggested several pathways leading to this relation. For example, carrying excess body fat multiplies mechanical stress on lower limbs and may induce knee and hip osteoarthritis and a chain of metabolic disorders such as dyslipidemia, atherogenesis, diabetes or hypertension, which in turn predict muscle weakness and mobility limitations.

Previous investigations showed that genetic influences explain variability in both mobility and obesity phenotypes. About 35% of the variability in walking ability phenotypes among older men and women was explained by additive genetic influences, while for obesity the corresponding proportion varied between 40% and 80%. The aim of the present study was to examine the extent to which common genetic and environmental factors explain the cross-sectional and longitudinal association between measures of walking ability and obesity in older women living in the community.

This research is part of the Finnish Twin Study on Aging (FITSA). The study sample consisted of 103 monozygotic and 114 dizygotic pairs of twin sisters reared together, with ages from 63 to 76 years in 2001. Longitudinal data on body mass index (BMI) was gathered in 5 waves (years 1975, 1981, 1990, 2001 and 2004). Further data on body fat percentage (bioimpedance test) was gathered in 2001. Mobility was evaluated in 2001 and 2004, using tests on maximal walking speed over 10 meters and distance walked in 6 minutes. Genetic and environmental influences on each trait and their relation were estimated using different multivariate, age-adjusted genetic modeling techniques.

The heritability of BMI showed a consistent increment across occasions, from 54% in 1975, to 72% in 2004. The heritability of walking endurance also increased from 40% in 2001, to 60% in 2004, while the heritability of walking speed remained stable at around 55-60% level between 2001 and 2004.

Cross-sectional and longitudinal multivariate analyses confirmed that among community-living older women, there was an inverse association between obesity and mobility phenotypes. These cross-sectional and longitudinal associations were mostly due to the effect of shared genes, and so the genetic influences predisposing to obesity in middle and old age increased the risk for poorer mobility later in life. These results imply that identifying genetic variants for obesity may potentially lead to interventions targeted at preventing excessive weight gain and its potentially negative sequelae in the physical health of the older population.

Keywords: Longitudinal, Heritability, Obesity, Mobility, Aging, Older female twins

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Ithaka

Lähtiessäsi Ithakaan
Sinun tulee ruoilla, että matka olisi pitkä,
täynnä seikkailuja ja kokemuksia.
Laistrygonit, kykloopit,
vihainen Poseidon – älä pelkää niitä,
et tule koskaan löytämään mitään sellaista matkallasi,
jos vain ajatuksesi ovat jaloja
ja varjelet tunteita, jotka koskettavat sieluasi ja
ruumistasi.
Laistrygonit, kykloopit,
riehuva Poseidon – et koskaan kohtaa niitä
ellet kuljeta niitä sielussasi,
ellei sielusi nostata niitä eteesi.

Sinun täytyy rukoilla, että matka olisi pitkä.
Kesäaamuin laskeudu satamiin,
joita et ole koskaan aikaisemmin nähnyt,
nauttien ihastuneena; sinun täytyy
pysähtyä foinikialaisten kauppapaikkoihin
ja ostaa hyviä tavaroita, helmiäistä ja korallia,
meripihkaa ja norsunluuta,
kaikenlaisia aisteja kiihottavia tuoksuvia öljyjä,
niin paljon kuin näitä voit vain hankkia;
sinun täytyy mennä moniin Egyptin kaupunkeihin
yhä vielä oppimaan niiltä, jotka tietävät.

Sinun täytyy aina pitää Ithaka mielessäsi,
sinne saapuminen on sinun päämääräsi.
Mutta älä lainkaan kiirehdi matkallasi.
On parempi, että se kestää monta vuotta:
ole vanha kun ankkuroit saaren rantaan,
rikkaana kaikesta, minkä olet saavuttanut matkalla,
sillä älä odota Ithakan antavan sinulle rikkauksia.

Ithaka on antanut sinulle loistavan matkan.
Ilman Ithakaa et olisi koskaan lähtenyt liikkeelle.
Ithakalla ei ole sinulle enää mitään annettavaa.
Vaikka saari onkin köyhä, Ithaka ei ole pettänyt sinua.
Olet tullut viisaaksi, olet kokenut,
ja silloin olet ymmärtänyt Ithakan merkityksen.

Ithaca

As you set out for Ithaka
hope your road is a long one,
full of adventure, full of discovery.
Laistrygonians, Cyclops,
angry Poseidon - don't be afraid of them:
you'll never find things like that one on your way
as long as you keep your thoughts raised high,
as long as a rare excitement
stirs your spirit and your body.
Laistrygonians, Cyclops,
wild Poseidon - you won't encounter them
unless you bring them along inside your soul,
unless your soul sets them up in front of you.

Hope your road is a long one.
May there be many summer mornings when,
with what pleasure, what joy,
you enter harbours you're seeing for the first time;
may you stop at Phoenician trading stations
to buy fine things,
mother of pearl and coral, amber and ebony,
sensual perfumes of every kind -
as many sensual perfumes as you can;
and may you visit many Egyptian cities
to learn and go on learning from their scholars.

Keep Ithaka always in your mind.
Arriving there is what you're destined for.
But don't hurry the journey at all.
Better if it lasts for years,
so you're old by the time you reach the island,
wealthy with all you've gained on the way,
not expecting Ithaka to make you rich.

Ithaka gave you the marvellous journey.
Without her you wouldn't have set out.
She has nothing left to give you now.
And if you find her poor, Ithaka won't have fooled you.
Wise as you will have become, so full of experience,
you'll have understood by then what these Ithakas mean.

Constantine P. Kavafy

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LIST OF ORIGINAL PUBLICATIONS

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ABBREVIATIONS

A	Additive genetic effects
ACE	Angiotensin I converting enzyme
ADL	Activities of daily living
ADRB2	b_2-adrenergic receptor
AIC	Akaike information criterion
ApoE	Apo-lipoprotein E
BIC	Bayesian information criterion
BMI	Body mass index
C	Common environmental effect
CART	Cocaine- and amphetamine-regulated transcript
CFI	Comparative fit index
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
D	Dominance genetic effects
DEXA	Dual Energy X-ray absorptiometry
DNA	Deoxyribonucleic acid
DZ:	Dizygotic
E:	Specific environmental effects
FAS:	Fatty acid synthase
FITSA:	Finnish Twin Study on Aging
FS:	Frailty syndrome
GNB3:	Guanine nucleotide binding protein, beta polypeptide 3
h^2:	Heritability estimate
IL:	Interleukin
ICC:	Intra-class correlation coefficient
MZ:	Monozygotic
MRI:	Magnetic resonance imaging
%BF:	Percentage of body fat
MC4R:	Melanocortin 4 receptor
PGC-1α	Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha
R^2	Regression coefficient
r	Correlation coefficient
r_g / r_e	Correlation of genetic / non-shared environmental factors
RMSEA:	Root mean square error of approximation
SRMR:	Standardized root mean residual
TNF-α:	Tumor necrosis factor alpha
V_P:	Phenotypic variance
V_G:	Genetic variance
V_E:	Environmental variance
WHO:	World Health Organization
WHR:	Waist-to-hip ratio
UCP-2 / UCP-3	Uncoupling protein 2 / Uncopupling protein 3
-2LL:	-2 times log-likelihood

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1 INTRODUCTION

Increasing adult life expectancy and greater numbers of people surviving into old age is a global phenomenon in both developed and developing countries (Ebrahim et al., 1996). Although older adults are healthier today than ever before (Koskinen et al., 2006), diseases, impairments, limitations and disabilities tend to increase with age. In the Finnish nationwide Health 2000 survey, 2% of the individuals aged 55-64 years had difficulties to walk at a normal pace of 0.8 m/s, while the corresponding proportion increased to 25% in the age range of 75-84 (Aromaa et al., 2002). Mobility limitations and disability seriously compromises independence and quality of life in older men and women (Ostir et al., 1998). Identifying the underlying causes of differences in mobility between persons is, therefore, essential to understand aging and a key element to responding to the population-ageing phenomenon.

Obesity has been acknowledged as a major risk factor for mobility limitations and disability in older men and women (Zamboni et al., 2005). In Finland, the *Health 2000* survey showed that the population segment in Finland with the highest prevalence of obesity consists of adult around the retirement age. About 28% of men and 34% of women aged 55-64 years were obese (Aromaa et al., 2004). This excess of body weight may potentially have adverse sequelae on health later in life. Overweight and obesity are considered major risk factors for cardiovascular disease, different types of metabolic diseases ("NIH Publication No. 98-4083," 1998) and an earlier onset of functional limitations (Sternfeld et al., 2002, Al Snih et al., 2005).

Obesity and mobility limitations are often concomitantly present, particularly in older population. Up to present, this link between obesity and mobility has been mainly explained by the interaction of several environmental factors such as physical activity or eating habits (Morgan et al., 2000). For example, persons with little physical activity habits tend to develop higher body weight, lower physical fitness and poor functional capacity, which makes them to be still less active, gain more weight and enter into a vicious circle. There have been suggested other pathways, and for example, higher body weight to carry as such causes increased wear and tear on joints and reduces

flexibility. Those persons with higher body weight shows increased energetic demands for a given activity compared to the normally weighted persons, which poses further metabolic difficulties to move.

As genetic influences explain also the individual differences in obesity and walking ability, it is intuitive that genetic factors may mediate the association between mobility and obesity. Previous reports showed that 40-80% of the variability in measures of obesity among older men and women were explained by additive genetic influences (Schousboe et al., 2004, Hsu et al., 2005), while for walking phenotypes, the corresponding proportion varied between 11% to 32% (Carmelli et al., 2000a, Leinonen et al., 2005, Pajala et al., 2005). To the present, precise information on the extent of a genetic relation between adiposity and mobility performance in humans is very limited, and only previous animal studies have clearly evidenced a potential genetic mechanism in common, with increased body weight in rats that were selectively bred for low physical fitness and reduced mobility (Wisloff et al., 2005).

The aim of the present study was to examine the genetic and environmental influences on mobility, obesity and their association in older, community dwelling women, using both cross-sectional and longitudinal twin data.

2 LITERATURE REVIEW

2.1 Basics of genetics of complex traits

2.1.1 Genes and inheritance

Humans have sensed biological transmission and heritage from long time ago (Jansson, 2004). It was not until the 19th century when heredity got the attention of scientists. In 1859, Charles Darwin (1809-1882) published the Evolution Theory, suggesting the importance of knowing the principles behind inheritance. Almost simultaneously, in 1866, Gregor Mendel (1822-1884) experimented with pea plant breeding to conclude that offspring may inherit heritable factors following predictable patterns, each of them responsible for a specific character. Soon after, Francis Galton (1822-1911) applied statistical methods to the study of inheritance and human differences among family relatives and twin brothers and sisters.

The term *genetics* appeared in 1909 when the Danish biologist Wilhem Johansen (1857-1927) named the Mendel's heritable factors as *genes*. Nowadays a gene is commonly defined as a single unit of hereditary material that corresponds to a segment of DNA (Jansson, 2004). In 1953, James Watson (1928-) and Francis Crick (1916-2004) described the building blocks of heredity, DNA, as a macromolecule with double-helical structure consisting of two strands of repeating units called nucleotides (Watson et al., 1953). Each nucleotide is made of five-carbon sugar (deoxyribose), a phosphate group and a nitrogen base. In the draft of the human genome presented in 2001, around 3.3 billion of nitrogen bases were detected (Lander et al., 2001).

Genes are disposed linearly along each chromosome. Chromosomes are small threadlike structures made up of DNA that are contained within the cell nucleus. A human cell contains, in overall 22 pairs of chromosomes (or autosomes, numbered from 1 to 22), and two sex chromosomes (denoted as X and Y). We inherit from each parent 22 autosomes and one sex chromosome, to a total of 46 chromosomes (Ford et al., 1956, Levan, 1956). Together these 46 chromosomes contain an estimated 20,000–25,000 protein-coding genes.

A gene is placed on a specific region of DNA within a chromosome, known as *Locus*. Variants of the DNA sequence at a locus are known as *alleles*. In overall, every gene has coding sections (exons) and non-coding sections (introns) of variable length, from thousands to millions of nitrogen base pairs. The functional constraints on the length or sequence of introns are not well understood. Nitrogen bases in a gene code for amino acids. The order of bases in a gene gives the structured chain of amino acids that produce a working protein. Genes that code for a protein are named *structural genes*. There are also regions of DNA with unidentified function named as *pseudogenes, processed pseudogenes or repeats*. It is estimated that 90% of the billions of nitrogen base pairs do not carry actively coding information (Strachan et al., 1996).

Structural genes do not change in response to the environment but rather formulate their product regardless of the environment. On the contrary, the vast majority of the genes are called *regulatory genes*, and they code for products that bind with DNA itself and serve to regulate other genes (Griffiths, 2004). These genes are responsible for the communication with the environment. The transcription of most of the structural genes is controlled by regulatory genes and so they adapt their response to the environment both inside and outside the cell. There are several other regulatory mechanisms for the expression of genes, such as *enhancer sequences* or also *histones* (Wasylyk, 1988) (Rogers et al., 1986). Enhancer sequences may be activated by the presence of environmental triggers such as heat shock, exposure to heavy metals, and viral infections, while histones are highly involved in the initiation or repression of genetic transcription (Grunstein, 1992).

Diseases with genetic etiology may occur for instance, due to changes or damages in a DNA sequence, or so-called *mutations*. When mutations happen in a germ cell they may be randomly passed into the next generation following a Mendelian inheritance pattern in a dominant way (the mutation is necessary to be only in a chromosome within a pair to cause a disease phenotype), or a recessive (both chromosomes within a pair need to carry the mutation to cause the disease phenotype).

2.1.2 Quantitative genetics and the study of complex phenotypes

Common diseases such as type-2 diabetes or hypertension are to some extent hereditary. However, their patterns of inheritance are not consistently clustered in families, but rather caused by the effect of multiple genes (additively or non-additively) that may interact with environmental stressors. They are named *complex diseases* and their measures *complex phenotypes* (the term *complex* here implies that a trait is influenced by many factors).

Complex phenotypes are usually measured as a continuum of a range of values. When an individual exceeds a determined threshold for a measure describing a phenotype, he/she is considered as affected by a disease. For example, obesity is often expressed as percentage of body fat that ranges from a population minimum to a maximum; a woman with more than 33% of body fat is usually considered as obese (Wellens et al., 1996). Inter-individual differences

and variability in these phenotypes within populations is constantly present and inheritance in complex phenotypes denotes DNA differences transmitted from generation to generation (Plomin, 1994). In statistical terms, the study of heredity is the study of the underlying causes of the population variance. Therefore, for a given trait, it is considered that most of the individuals' values in a population are around a mean level, and inter-individual variability is normally distributed.

Quantitative genetics is the discipline studying how much of the inter-individual variability within a population can be attributed to genetic and to environmental factors (Plomin, 1994). The methods of quantitative genetics decompose the observed variation for a phenotype *(V_P)* into genetic *(V_G)* and environmental *(V_E)* components of variance.

Equation 1 $V_P = V_G + V_E$

The genetic contribution to a phenotype may be decomposed in additive genetic variability (A), reflecting the addition of the effects of multiple genes at different loci, and dominance genetic variance (D), reflecting the effects of multiple genes at a single locus. The addition of A and D is known as *broad sense heritability (h^2)* while the A alone is referred as *narrow sense h^2*.

Equation 2 $h^2 = \frac{(A+D)}{V_P}$

In absence of genetic dominance, broad sense and narrow sense h^2 are essentially the same. The concept of h^2 should be regarded as a probabilistic tendency, rather than predetermined programming. Estimates are population and time specific.

Environmental factors can be decomposed as shared (C) and non-shared (E) environmental variance. C refers to the environmental variation contributing to similarities within family members, while E corresponds to the environmental variation causing differences within family members. Thus, when a phenotype is aggregated within families, it may be only due to the contribution of both genetic and common environmental factors.

2.1.3 The study of heredity using twin brothers and sisters

Twin studies are a particular scientific design mainly characterized by the fact that the study sample comprises solely twin brothers and sisters. The modern history of twin studies derives from Sir Francis Galton's when in the 1870s he published a series of articles arguing that heredity was a stronger factor than environment in determining the respective characteristics of twins. The systematic analysis of similarities between MZ and DZ twins was firstly introduced in the 1920s by the ophthalmologist Walter Jablonski in Germany, and later by the dermatologist Herman W. Siemens. In 1922, Jablonski published a manuscript entitled "Ein Beitrag zur Vererbung der Refraktion menschlicher Augen" (English translation: A contribution to the heredity of refraction in human eyes), in which he used both MZ and DZ twins to examine

refractive error in twins (Jablonski, 1922, Liew et al., 2005). Later, in 1924, Siemens formulated in his book "Die Zwillingspathologie", the twin rule of inheritance: any heritable trait will be more concordant in MZ than in DZ twins, and less concordant still in non-siblings (Siemens et al., 1924, Spector et al., 2000).

The method was extended successfully in the 1930s by a group of researchers at the University of Chicago, among who were Horatio H. Newman, Frank N. Freeman and Karl J. Holzinger (Lindee, 2005). This group developed the methodology using for instance a 10-years classical twin study including 100 twin pairs, or a small MZ twin adoption study including 19 pairs (Newman et al., 1937). Those researchers had different interests and while Newman's focus was on developing methods to study MZ twins reared apart, Holzinger, in contrast, was concerned in developing analysis of variance methods to estimate the heritability of different traits, which were in use until the 1970s (Duffy, 1994). Nowadays the twin methodology is worldwide known and probably the most used in quantitative genetics.

The fundaments of this classic twin method are based on the comparison of twin brothers or sisters. Twins are either dizygotic (DZ, commonly referred to as fraternal) or monozygotic (MZ, identical). Approximately one in every eighty births results in the delivery of twins (Jansson, 2004), and MZ twinning accounts for approximately 35% of twin births (Bamforth et al., 2004). MZ twins are the result of one egg fertilized by a single sperm. The fetus splits in two around the time that the fertilized egg is implanting in the womb. The DZ twins are the result of two different eggs being fertilized by two separate sperm and resulting in two completely distinct and separate pregnancies in the womb at the same time. Thus, MZ twins are genetically identical and necessarily concordant for any inherited characteristic, while DZ twins share on average half of their genetic background.

In the 1960s decade, the British geneticist Douglas S. Falconer proposed a simple algebraic formula based on the observed within-pair correlations in MZ (r_{mz}) and DZ (r_{dz}) twins, to estimate the broad sense h^2 for given trait (Falconer, 1960):

Equation 3 $$h^2 = 2(r_{mz} - r_{dz})$$

Assuming that environmental effects influence equally MZ and DZ twins, greater resemblance between MZ than DZ twin pairs for a given phenotype will be suggestive of genetic effects. The r_{mz} is due to their totally shared genes (or h^2) and common environmental factors (C).

Equation 4 $$r_{mz} = h^2 + C$$

The r_{dz} is due to half of their inherited influences plus the effect of C.

Equation 5 $$r_{dz} = \frac{1}{2}h^2 + C$$

Differences within MZ twins are only due to the specific (non-shared) environmental influences (E), while differences within DZ twins are due to

their differences in genes and in specific environmental influences. Based on the aforementioned formulas, and by simple rules of equating, C and E can be estimated as follows:

Equation 6 $C = 2r_{dz} - r_{mz}$

Equation 7 $E = 1 - h^2 + C$

When the r_{mz} equals the r_{dz}, then h^2 is 0 and the variance is completely attributed to environmental factors. If r_{mz} doubles the r_{dz}, it is considered that there are evidences for genetic dominance (D) within the phenotype.

2.1.4 The biometric methods

In the 1970s, twin research transitioned to complex statistical methods explicitly modeling the values of A, D, C, and E within a maximum likelihood framework (Martin et al., 1977). Nowadays the estimation of the genetic and environmental influences is done using path analyses based on *biometric methods* (Neale et al., 1992).

Considering the fact that MZ twins share 100% of their genes, and DZ twins share on average 50% of their segregating genes, the essential path diagram underlying the relation between twin brothers / sisters can be described as in figure 1.

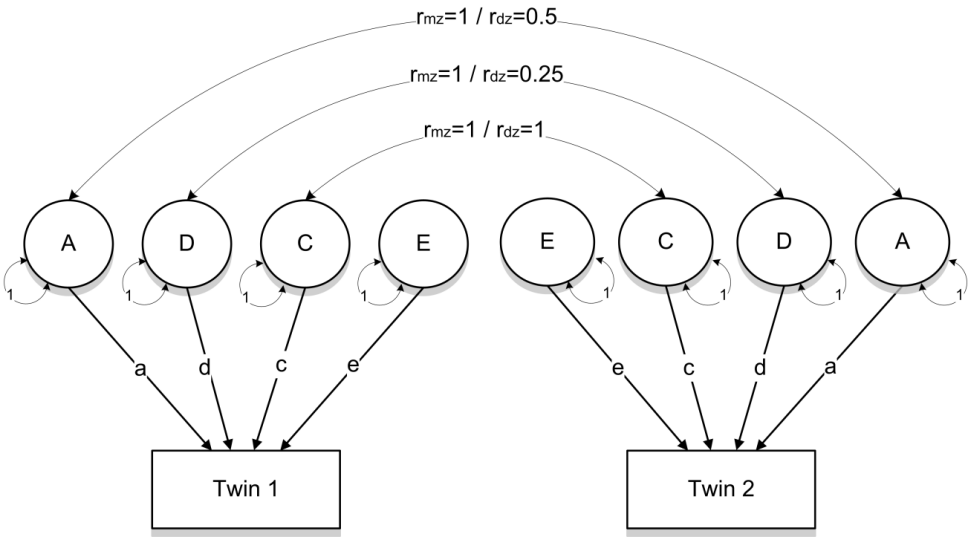


FIGURE 1 The within-pair relation between twins following path analyses

A and D contribute totally to within-pair similarities in MZ ($r_{A\text{-}mz}$=1; $r_{D\text{-}mz}$=1), but only half and one fourth, respectively, in DZ twins ($r_{A\text{-}dz}$=0.5, $r_{D\text{-}dz}$=0.25). C contributes equally to the similarities in MZ and DZ ($r_{C\text{-}mz}$=1; $r_{C\text{-}dz}$=1). E contributes only to within-pair differences for MZ and DZ twins.

Instead of using only pairwise concordances as in Falconer's equation, the biometrics method can utilize large amount of observed phenotypic data more effectively to obtain estimates of A, D, C and E for a trait by using information on the twin and co-twin covariance structure, and comparing observed and expected variance-covariance matrices. Different combinations of values for the model parameters will generate different expected variance-covariance matrices. This iterative method allows testing for the best fitting model to obtain estimates of the variance components for a phenotype generating also confidence statistics for all the estimated parameters. Iterative programs such as MX (Neale, 1997) will evaluate the statistical appropriateness of the result once suitable starting values and model expectations are defined, by providing fitting statistics for all models tested, including for instance the χ^2 statistic (as a function of the sample size and the difference between the observed covariance matrix and the model covariance matrix), maximum likelihood values, the Root Mean Square Error of Approximation (RMSEA), the Standardized Root Mean Residual (SRMR), the Comparative Fit Index (CFI), the Akaike Information Criterion (AIC) or the Bayesian Information Criterion (BIC). Model selection is normally based on the comparison of fitting statistics following *Occam's Razor* or the Principle of Parsimony: always prefer a simpler explanation if it accounts equally well for the observations. Once fitting statistics for a model in which all-possible variance components are estimated (that is, ACE or ADE model), a model will be built with lower number of estimated parameters (e.g. AE, DE, CE or E models). They are called nested models and their appropriacy needs to be tested against the full models. The final result for the studied phenotype is normally chosen among the theoretically acceptable models with as few parameters as possible, but still providing a relatively good fit to the data compared to the model with all possible paths estimated.

An extension to the single phenotype study in biometric methods is the multivariate modeling, in which more than one phenotype per person is studied simultaneously. Multivariate analyses are important because they can carry simultaneous modeling of phenotypes and endophenotypes or intermediate phenotypes to determine possibly common genetic etiology or pleiotropic genetic effects. For example, multivariate analyses carried by Kendler et al and Roy et al found that the association between depression and anxiety was not due to chance or a third independent factor, but rather to underlying genes common to both traits (Kendler et al., 1993, Roy et al., 1995).

By definition, estimates of genetic and environmental influences are considered population-, age- and, in some cases, gender- specific. Genetic influences on a given trait in younger cohorts may show differently than in older ones. For example, the heritability for cholesterol and blood lipids seems to be lower in younger individuals. For other traits, such as cognitive ability or life satisfaction, the importance of heredity increases over years, though it may also remain stable, as in the case of some personality traits (Pedersen et al., 1991, Finkel et al., 1998, Pedersen et al., 2003).

Nowadays, the twin methodology contributes to provide essential understanding of developmental and aging traits. A rich variety of twin studies have provided evidences of genetic and environmental influences on aspects related to physical and mental health, using both cross-sectional and longitudinal analytical frameworks. In Europe, a number of twin registries have assembled data from questionnaires directed at a large number of twin pairs. The large population-based twin registries or cohort studies in Scandinavia (Finnish Twin Cohort Study, Norway Twin Panel, Swedish Twin Registry and Danish Twin Registry) are well known, but large population-based or volunteer twin studies now also exist in Germany, Belgium, the UK, Italy and The Netherlands (Boomsma, 1998).

2.2 Mobility in older age

Walking ability is essential for preserving autonomy in the community and is a major determinant of health and quality of life in aging. Older persons with walking limitation are at increased risk of loss of independence and social isolation (Bootsma-van der Wiel et al., 2002). Poor ability to walk is related to recurrent falls, poor health and shorter survival, poor life satisfaction, disability and increased need for care.

Ability to walk in older persons can be evaluated using different methods, depending on the available equipments, room, time, personnel and financial resources. The spectrum of available procedures encompasses *self-reported* and *performance-based* measures. The first relies on self-reports of difficulties in activities such as walking across a small room, walking outdoors or negotiating stairs. Individuals provide answers to questions concerning their difficulties in walking a particular distance, e.g. 400 meters (Rantanen et al., 1999b), 500 meters (Aromaa, 1989), 800 meters (Guralnik et al., 1994, Reuben et al., 2004) or 2000 meters (Haapanen-Niemi et al., 2000, Manty et al., 2007). Respondents usually are also asked whether they can perform these activities with or without the help of someone else, or the use of a special device (Wolinsky et al., 1992, Jette, 1994). Self-reported walking ability is a good predictor of future disability and mortality in older individuals (Haapanen-Niemi et al., 2000, Reuben et al., 2004).

A second approach to the evaluation of walking ability measures directly an individual's ability to perform a walking task (Guralnik et al., 1989, Cress et al., 1995). Their evaluations are often referred as *performance-based* tests. Among the performance-based assessments, tests on either walking speed or endurance capacity are often used. There are several versions of the walking speed tests, either measuring customary speed over the distances of 8 feet (2.4 meters) (Guralnik et al., 1994), 10 feet (3 meters) (Angel et al., 2000), 4 meters (Rantanen et al., 1999a) and 20 feet (6.1 meters) (Bassey et al., 1992); or measuring maximal speed over distances of 25 feet (7.6 meters) (Schwid et al., 2002) and 10 meters

(Sakari-Rantala et al., 1995, Tiainen et al., 2007). While the customary speed tests normally show the normal performance level in everyday life, the maximal speed tests generally capture the highest neuromuscular capacity developed, offering an idea of the individual's possibilities to adapt to different physical demands.

Detailed characteristics of walking are also studied utilizing complex technological devices such as force platforms and computerized movement analyses. These sophisticated laboratory assessments can provide objective computerized gait analysis, giving accurate information of temporal measures, kinematics (limb motion assessed by the use of motion analysis systems and markers across joints), electromyography and kinetics (forces exerted by body using in-ground force plate transducers) (Pearson et al., 2004). These techniques may provide valuable information to evaluate the components of impaired walking in an individual, yet they are labor intensive and costly, and therefore not commonly used in studies involving large groups of persons.

Walking tests over longer distances have also been used with clinical and experimental purposes in order to capture endurance characteristics in this ability (e.g. cardio-respiratory status). Among the most commonly reported is the 6-minutes walking test, and it is considered as a valid and reliable test to assess functional capacity, sub-maximal exercise capacity and cardio-respiratory status (Lipkin et al., 1986, Bean et al., 2002, Enright et al., 2003). Other tests also commonly reported in the literature are the 3-minutes (Iriberri et al., 2002) or 12-minutes (Cooper, 1968) walking tests, the long-distance (400-meters) corridor test (Simonsick et al., 2001) or the shuttle walk test (Revill et al., 1999).

The main difference between self-reported and performance-based measurements relies on their different sensitivity to identify levels of mobility (Angel et al., 2000). There is often only a moderate concordance between the results of the two approaches. Self-report and performance based measures provide relatively different, independent and useful information (Jette et al., 1985, Kelly-Hayes et al., 1992, Sager et al., 1992, Myers et al., 1993, Rozzini et al., 1993, Verbrugge et al., 1994, Cress et al., 1995, Reuben et al., 1995, Kempen et al., 1996).

There are also practical considerations that differentiate both approaches. The self-reported measures of walking are generally based on questionnaires or interviews and are often used in epidemiological studies involving large samples. On the other hand, physical performance measures have important clinical as well as epidemiological utility, and they have proved highly valid, quick, inexpensive, sensitive and reliable (Cesari et al., 2005). In comparison to self-reported measures, however, physical-performance ones are more difficult to administer, require special equipment and training, and are in general more expensive in time and money.

The prevalence figures on walking difficulties and disability may vary slightly from country to country depending on the estimating method used. In the United States of America, the U.S. National Health and Nutrition Examination Study (NHANES III) identified that the incidence of severe

walking difficulties among women (defined as the inability to walk 400 meters and a walking speed less than 0.4 m/s or being unable to walk) was 2.0% for ages 65 to 74 years, 3.4% for ages 75 to 84 years and 9.1% for age 85 years and older (Rantanen et al., 2001). In the UK, the Continuous Household Survey showed that 12% of the men and 10% of the women aged 55 to 64 had mobility difficulties somewhat limiting outdoor actions, while the percentage increased to 21% of the men and 38% of the women aged 75 years and older ("Continuous Household Survey Bulletin 2005/2006," 2006). In Finland, the *Health 2000* survey indicated that the incidence of difficulties in walking a distance of 500 meters was 8% in men and women aged 55 to 64 years, while the percentage increased to 18.3% in men and 23.1% in women aged 65-74 years, and to 41% of men and 52% of women aged 75 to 84 years (Heistaro, 2005).

2.2.1 Changes in mobility with age

Longitudinal and cross-sectional data indicate that mobility tend to decrease with increasing age. For example, Bohanon et al. showed that average maximal walking speed in healthy men and women in their 30s were 2.5 and 2.3 m/s respectively, while the corresponding values among men and women in their 60s decreased to 2.0 and 1.7 m/s, respectively (Bohannon et al., 1996, Bohannon, 1997). In the Finnish nationwide *Health 2000* survey, 2% of the individuals aged 55-64 years had difficulties in walking at a normal pace of 0.8 m/s, while the corresponding proportion increased to 25% in the age range of 75-84 (Aromaa et al., 2002). Poor walking ability is also considered an indicator of the frailty syndrome (FS), a geriatric syndrome of physical vulnerability characterized by multisystem dysfunction and lack of physiological reserve that appears progressively in old age (Fried et al., 2001, Morley et al., 2002, Bandeen-Roche et al., 2006, Morley, 2008). Other indicators of the FS are unintentional weight loss, muscle weakness, low physical activity and exhaustion (Blaum et al., 2005).

The causes for these changes in mobility are still not completely understood. Walking is a multifactorial task relying on physiological and psychological characteristics of every individual. Restrictions on these physiological and psychological prerequisites appear with increasing age, potentially leading to subsequent mobility limitations and disabilities. Nevertheless, important variability has been observed in this disability process from person to person, and individuals of the same age may differ substantially from each other in mobility. This variability is suggested to result from a longitudinal interplay of underlying genetic and environmental influences eventually expressing in the mobility phenotype (Bouchard, 1993).

The physiological factors on mobility include the coordination of the musculoskeletal, cardio-respiratory and senso-neural systems. For example, walking requires a sufficient level of lower-extremity muscle strength and balance to keep an upright position while moving forward (Rantanen et al., 1999a). With increasing walking velocity, the load on muscle response at higher speeds is also increased, and therefore sufficient muscle power capacity is also needed. In addition, range-of-motion (ROM) in lower extremity joints is also

associated with walking. Levels of muscle strength, muscle power or leg-joints ROM tend to decrease with age, and when they are below certain physiological or anatomical levels walking impairments may appear. Besides, increasing walking distance amplifies the metabolic and cardiovascular demands for the task. As a consequence, individuals with metabolic deficiencies or lowered cardiopulmonary capacity normally show poor walking endurance ability (Cahalin et al., 1996, Peeters et al., 1996, Bean et al., 2002, Enright et al., 2003).

The psychological determinants of mobility compel different aspects of cognition and sensorial function, such as memory, visuo-spatial skills, cognitive processing speed, and executive control functions (Atkinson et al., 2007). For example, executive control function (ECF) involves attention, inhibition of distracting stimuli, and planning and execution of tasks. Recent research suggests that ECF mediates the stability and velocity of gait in older persons through its role in maintaining attention to walking and inhibiting distracting stimuli (Coppin et al., 2006, Holtzer et al., 2006, Springer et al., 2006, Atkinson et al., 2007). Further analyses using functional magnetic resonance imaging indicated greater cognitive monitoring of movements in old adults versus young adults, due for instance to differences in sensory status (Heuninckx et al., 2005).

Chronic diseases and different medical conditions also predict walking ability and mediate the impact of the physiological and psychological determinants of mobility. For example, cardiovascular pathologies or related degenerative lesions may affect both cognitive functions and physical performance. Lower extremity peripheral arterial disease is a chronic condition that severely compromises mobility and functional capacity due to intermittent claudication (Newman et al., 2003). Fatal events such as myocardial infarction, angina pectoris or stroke consistently predict declines in mobility (Cahalin et al., 1996, Dean et al., 2001). Neurological disorders such as multiple sclerosis or Parkinson's disease often culminate in abnormal or reduced walking as a result of different underlying processes. For instance, in multiple sclerosis, walking difficulties may arise from weakness and spasticity from pyramidal tract lesions, loss of proprioception and co-ordination from dorsal column and cerebellar lesions, vestibular and visual dysfunction, cognitive and mood disturbance and pain (Pearson et al., 2004). Rheumatic or arthritic diseases usually cause chronic pain, stiffness, and swelling in the joints and other supporting body structures, such as muscles, tendons and ligaments, which may restrict mobility in different ways (Daltroy et al., 1992, Odding et al., 2001, Bootsma-van der Wiel et al., 2002). While osteoarthritis for instance may affect mobility mainly by reducing ROM and muscle strength in the hip and knees (Steultjens et al., 2000, Lin et al., 2001), other disorders such as fibromyalgia may do it mostly by increasing muscle pain and stiffness (Tomas-Carus et al., 2007). In addition, obesity has been acknowledged as a major risk factor for mobility limitations in older men and women and is considered a growing medical concern in most western countries (Zamboni et al., 2005). At present, the information on the underlying mechanism leading to the relation between mobility and obesity is limited, although the mediation of common genetic and

environmental influences are suggested as key elements to understand this issue.

2.2.2 Genetic influences on mobility in adults and older

Evidences gathered through the past decades have indicated that genetic influences contribute to walking ability and its pre-requisites (Christensen et al., 2000). Research in this area has been done using different approaches. Twin and family studies have shown that, in overall, the contribution of heredity to physical function and other related phenotypes is moderate to high (Finkel et al., 1995, Bouchard et al., 2000, Carmelli et al., 2000a, Carmelli et al., 2000b, Frederiksen et al., 2002, Frederiksen et al., 2003, Tiainen et al., 2004). A relatively small group of studies have focused specifically on the genetics of mobility and walking performance in the older population. In the study of Carmelli et al, genetic influences accounted for 51% of variability in customary walking speed over 4 meters in older men (Carmelli et al., 2000a). Tiainen et al. found also a genetic influence of 34% for maximal walking speed over 10 meters in older women (Tiainen et al., 2007), while Pajala et al, suggested also heritability estimates of around 19-22% for maximal walking speed over 10 meters with a second task (Pajala et al., 2005). In overall, less is known about the genetics of walking over distances longer than 10-meters and about the stability and change of these influences with increasing age.

Other investigations have contributed importantly by studying the genetics of a variety of intermediate phenotypes or pre-requisites for walking, regarding respiratory function (Bouchard et al., 1998), neuromuscular and flexibility condition (Perusse et al., 1987, Arden et al., 1997, Thomis et al., 1997, Carmelli et al., 2000a, Katzmarzyk et al., 2001), as well as other applied traits such as activities-of-daily living (Fox et al., 1996, Thomis et al., 1998, Christensen et al., 2000, Christensen et al., 2002)(see table 1). For example, among adult and older women genetic influences accounted for up to 35% of upright balance (Pajala et al., 2004), 52% for isometric knee extension strength (Tiainen et al., 2007), 78% of explosive strength or 30-50% of speed of limb movement or reaction time (Maes et al., 1996, Simonen et al., 1998).

TABLE 1 Twin studies reporting on genetic influences for mobility and related traits in adults

Author, year	N, sex, age *	Phenotype	Heritability #
Fagard et al, 1991	48, men, 18-31 y-o	Maximum oxygen uptake	20-66%
Reed et al, 1991	257, men, 59-70 y-o	Grip strength	65%
Sundet et al, 1994	1058, men	Maximum oxygen uptake	62%
Arden at al, 1997	353, women, postmenopausal	Grip strength Knee extension strength	36% 46%
Thomis et al, 1997	41, men, mean age 22.4 ± 3.7 y	Elbow flexion strength Muscle cross-sectional area	70% 92%
Thomis et al, 1998	41, men, mean age 22.4 ± 3.7 y	Trainability of muscle strength	20%
Carmelli et al, 2000	152, men, 63-73 y-o	Grip strength	22-35%
Carmelli et al, 2000	187, men, 68-79 y-o	Customary walking speed Chair stands Balance	Men 42% Men 46% Men 0%
Chistensen et al, 2000	480, men & women, +75 y-o	Activities of Daily Living (ADL)	Women 0% Men 34%
Chistensen et al, 2002	127, men & women, +75 y-o	Rate-of-change of self reported functioning	Women 16% Men 9%
Frederiksen et al, 2002	861 men & 896 women, 45-96 y-o	Grip strength	52%
Tiainen et al, 2006	217, women, 63-75 y-o	Maximal walking speed Isometric knee extensor strength Muscle leg extension power	34%, 52% 53%
Pajala et al. 2006	217, women, 63-75 y-o	Balance	Women 34%

*Number of twin pairs, sex and age range or average (in years-old) of the study sample; # Heritability estimates are often reported for more than one phenotype and after various adjustments and restrictions in the different studies

Further evidence of the genetic regulation of mobility are also available from studies at a molecular level. Linkage studies have acknowledged the effect of different genes on maximal oxygen uptake and exercise capacity, e.g. the skeletal muscle-specific creatine kinase gene (CKMM), the b-sarcoglycan gene (SGCB), the syntrophin b-1 gene (SNTB1), the c-sarcoglycan gene (SGCG), the dystrophin-associated glycoprotein 1 gene (DAG1), the lamin A/C gene (LMNA), the liver glycogen phosphorylase gene (PYGL), the guanosine triphosphate cy- clohydrolase I gene (GCH1), or the sulfonylurea receptor gene (SUR) (Bouchard et al., 2000).

A few genotypes have been already associated with decreased mobility and poor physical capacity. For example, in a recent study common inherited variants in the $p16^{INK4a}$/ ARF/$p15^{INK4b}$ genetic region and 3 related cyclin dependent kinase inhibitor genes (typically involved in triggering cell senescence) were associated with differences in physical functioning in older people aged 65–80 years (Melzer et al., 2007). In older persons, elevated interleukin (IL) -6 levels are inversely associated with muscle mass and strength, physical performance, balance, and walking speed, and positively associated with earlier mortality (Cohen et al., 1997, Visser et al., 2002b, Payette et al., 2003). Variants of the inflammatory marker IL-6 and -18 genotypes were also associated with measured functional impairments in older individuals (Frayling et al., 2007). Additional studies have suggested a genetic relation of mobility, physical activity and cognitive function by showing an ApoE ε4 polymorphism associated with both declines in cognitive function (Tilvis et al., 2004) and mobility performances in older individuals (Melzer et al., 2005).

Other genes influencing physical function and physical activity in adults and older are the angiotensin I converting enzyme (ACE) gene, the guanine nucleotide binding protein, beta polypeptide 3 (GNB3) gene, the b_2-adrenergic receptor (ADRB2) gene, MC4R, the cocaine- and amphetamine-regulated transcript (CART) gene, UCP-2 and UCP-3 genes (Montgomery et al., 1998, Otabe et al., 2000, Siffert, 2000, Buemann et al., 2001, Corbalan et al., 2002, Loos et al., 2005). For example, persons with the DD genotype of the ACE gene showed poorer endurance capacity than those with the II and ID genotype (Montgomery et al., 1998). A more detailed description of possibly related genotypes and genetic regions of interest can be found, for instance in the review from Rankinen and colleagues (Rankinen et al., 2006a).

2.3 Body weight, body composition and obesity

Body Composition is the term used to describe the different tissues configuring the human body. When evaluating body composition, tissues are sometimes grouped in two categories: *lean* tissues and *adipose* tissue. The so-called *lean* tissues include muscle, bone and organs, while the adipose tissues include body fat. Both these tissue types taken together make up a person's *body weight*. Although body weight is a good indicator of body size, it gives no specific information on the *relative weight* of the person or the tissue composition of the body. Thus, other methods than solely body weight are normally used to estimate body composition, such as measures of body fat percentage (%BF), body mass index (BMI) and waist-to-hip ratio (WHR).

The most sophisticated and accurate measures of body composition are given by dual energy x-ray absortiometry (DEXA), magnetic resonance imaging (MRI), computed tomography (CT) or bio-electrical impedance. These techniques determine the exact amount (percentage) and distribution of fat in each body compartment. Yet, most of these methods may not be available for every study, especially for those involving large populations, as they are relatively difficult to use and are expensive in time and money. The exception among these hi-tech measures is given by the bio-electrical impedance technique, which provides valid body composition estimates at comparatively low cost in time and money (Jebb et al., 1993, Kyle et al., 2004).

BMI is probably the most widely-used measure of body composition, and is readily available for both clinical and research purposes. This method represents a measure of relative body weight, and correlates relatively well with body fat percentage (Rosenbaum et al., 1988, Gray et al., 1991, Strain et al., 1992). BMI can be easily obtained by dividing weight in kilograms by height in meters squared (kg/m^2) ("Obesity: preventing and managing the global epidemic. Report of a WHO consultation," 2000).

In addition, WHR is a relatively easy measure of abdominal concentration of fat tissue and it is based on the evaluation of waist perimeters (at the

midpoint between the lower border of the rib cage and iliac crest) and hip (at the widest part of the pelvis). To determine the ratio, the waist is divided by the hip perimeter.

The World Health Organization (WHO) has defined that when relative body weight and body fat tissue are over certain point, there is evidence for a disease named *Obesity* ("Obesity: preventing and managing the global epidemic. Report of a WHO consultation," 2000). Men with more than 25% of total body fat and women with more than 33% of body fat are normally considered *obese* (Wellens et al., 1996, Jackson et al., 2002). The WHO has defined additional cut-off points for obesity based on other measures of body composition, such as WHR and BMI ("Obesity: preventing and managing the global epidemic. Report of a WHO consultation," 2000). The cut-off points using WHR are 1.0 in men and 0.85 in women. Regarding BMI, measures within 18-25 kg/m^2 are considered as *normal*, over 25 kg/m^2 as *overweight* and over 30 kg/m^2 as *obesity*.

The prevalence of overweight and obesity has been increasing in the recent decades within the population of most of the developed and developing countries. The highest prevalence rates among the developed countries, probably may be seen within the United States, with 54% of overweight adults and 22% obese (Flegal et al., 1998). Prevalence rates in Europe have been consistently rising in recent years, becoming in some countries similar to those in the US (Seidell, 1995). In Finland, obesity rates have been increasing during the last 30 years (Lahti-Koski et al., 2000), and nowadays obesity is considered a growing public health concern. According to the WHO observatory, in 2005 around 25% of the adult Finnish men and women aged 30 to 65 years were obese. In comparison, this rate is slightly higher than the European average and the highest among the Scandinavian countries. Obesity seems more common among older Finnish women (31%) than men (21%) (Aromaa et al., 2004). Severe and morbid forms of obesity are rare among Finns and for instance, in the 1990s only 3.0% of Finnish men and 5.5% of women were severely obese, while 0.5% of men and 2.1% of women were morbidly obese (Pietinen et al., 1996).

2.3.1 Changes in body weight and body composition with age

There are relevant changes in body composition that are associated with age. Cross-sectional and longitudinal data from large population studies have shown that body weight and BMI progressively increases across adult life, to reach a maximum between 60 to 70 years old (Villareal et al., 2005), and remain stable or decline afterward. The increase in BMI across adulthood is associated with an increase in the overall body fat percentage of around 1% per decade (Gallagher et al., 1996). Both intramuscular and intra-hepatic fat tend to increase gradually while fat-free mass (mainly muscle tissue) decreases, making central fat free mass relatively higher than peripheral fat free mass (Beaufrere et al., 2000). This age-related increase in body fat especially in the more internalized deposits, and the loss of muscle mass increase the risk of developing a wide

range of chronic metabolic disorders, including hypercholesterolemia, atherosclerosis, hyperinsulinemia, insulin resistance, type-2 diabetes and hypertension (Despres et al., 1990).

The causes of these longitudinal changes are yet not fully understood. In general, energy expenditure decreases with age. For example, basal metabolic rate, which account for 70% of the total expenditure, declines 3% per decade after the age of 20, while physical activity, which accounts for an additional 20%, tends also to decrease with age (Slingerland et al., 2007). These changes unbalance energy intake and expenditure, and in part are also mediated by hormonal alteration taking place with age and that are highly regulated by genetic networks. For instance, aging is associated with a decrease in growth hormone (GH) secretion, which is an important regulator of body composition, aerobic capacity, and metabolism throughout life. Other hormonal alterations are reduced responsiveness to thyroid hormone, decline in serum testosterone and estrogen or increased resistance to leptin. The production of these hormones is known to be determined by both genetic and environmental influences, and genes for example account for a substantial portion of variation in adult levels of human growth hormone (74%) (Mendlewicz et al., 1999), thyroid hormone (26–64%) (Samollow et al., 2004) or leptin levels (37%) (Kaprio et al., 2001).

Although it seems that genetic factors may play a major role in age-related changes in the metabolism and body weight regulation across adulthood, perhaps the more significant and controllable are the environmental factors, which include psychological, cultural, socio-economic and ecological determinants of diet and physical activity. For example, psychological aspects that have been related to overweight and obesity encompassed difficulties in controlling eating, feelings of hunger (Hakala et al., 1999), emotional eating (Lindroos et al., 1997) and binge eating (Wilson et al., 1993).

Socio-economial status may also play a role in obesity. Studies have reported a negative association between education and measures of obesity, indicating for instance that those persons with a lower level of education may show higher body weight (Nestle et al., 1998, Dastgiri et al., 2006). Income from salary or pension also plays a role in the occurrence of obesity, and it is suggested that being unable to afford fruits and vegetables in the daily diet or having supervised physical activity may contribute to increasing a person's risk for obesity (Popkin et al., 2005a, Popkin et al., 2005b, Dastgiri et al., 2006).

There are also further social, cultural and ecological factors that may promote weight gain with age. In overall, these social factors point towards an inefficient encouragement of healthy choices, with a lack of specific support from employers and companies, inadequate time to exercise due to family responsibilities, (King, 1997, Stewart et al., 1997, Brownson et al., 1998, Eyler et al., 1998, Brownson et al., 2000) or weak external motivation (perception of poorly motivating, unstable or discouraging atmosphere) (Eyler et al., 1998, Eyler et al., 2002b). Other major cultural factors may include unawareness of the importance of exercise and diet (Carter-Nolan et al., 1996), differing value ascribed to physical activity and diet (Airhihenbuwa et al., 1995), acceptance of

larger body sizes (Flynn et al., 1998), differing social norms, language barriers and culturally dictated familial roles (Eyler et al., 2002a). The living environment is also associated with important barriers to healthy choices. These may include for instance a lack of places to exercise safely in or to buy healthy foods from (Evenson et al., 2002, Sanderson et al., 2002, Thompson et al., 2002, Wilbur et al., 2002, Varo et al., 2003, Matson Koffman et al., 2005).

2.3.2 Genetic influences on the development of common forms of obesity

There is an overall consensus on the high degree of genetic control for obesity-related phenotypes. Overall, heritability estimates varied from 6% to 85% among various populations depending on gender, age and ethnicity (Yang et al., 2007).

Twin, adoption and family studies have provided the basis for the study of the genetics of common forms of obesity. Such studies started in the 1920s and during the following decades several articles were published on the issue, based on the weight for height data of study subjects (Bouchard, 1995).

The strongest evidence for a genetic contribution to obesity comes probably from twin studies. Initially, a high degree of genetic determination has been observed in adult and older twins' BMI, with most estimates in the range 0.50 – 0.90 (Stunkard et al., 1986a, Stunkard et al., 1986b, Maes et al., 1997). Table 2 summarizes the main results for BMI from a number of twin studies in the last 3 decades.

In additional studies of twins reared apart (in which the effects of shared environment is controlled) the heritability of obesity measures such as BMI remains within the same range (Stunkard et al., 1990). For example, in the study of Allison and colleagues, including twin pairs reared apart from Finland and other populations, the heritability estimates of BMI varied between 0.50-0.80 (Allison et al., 1996).

The changes across time in the genetic influences on obesity have been studied both cross-sectional and longitudinally. The cross-sectional analyses have suggested mostly decreasing heritability estimates with age (Korkeila et al., 1991). For example, the study of Danish twins including 535 male and 698 female pairs showed that females had greater heritability for BMI than males, and that heritability in males tends to increase with age (Herskind et al., 1996). The specific heritability estimates for BMI were 0.46 for adults and 0.61 for older males, and 0.77 for adults and 0.75 for older females.

TABLE 2 Twin studies reporting on the genetic influences on body mass index (BMI) in adults and older individuals

Author, year	N *	Heritability #		
		Men	Women	Overall
Feinlieb et al, 1977	514			64%
Fabsitz et al, 1980	1028	*20 y-o:* **80%** *25 y-o:* **67%** *40-50 y-o:* **51%** *42-56 y-o:* **57%**		
Stuntkard et al, 1986	4071			*20 y-o:* **77%** *25 y-o:* **84%**
Austin et al, 1987	434		**55%**	
Hunt et al, 1989	154	*+26 y-o:* **54%**		
Stunkard et al, 1990	311	**70%**	**66%**	
Stunkard et al, 1990	362	**74%**	**69%**	
Turula et al, 1990	7730	**72%**	**66%**	
Price & Gottesman, 1991	38			**75%**
Korkeila et al, 1991	7245	18-24 y-o: **72%** 25-34 y-o: **74%** 35-44 y-o: **67%** *45-54 y-o:* **67%** *Total:* **72%**	*18-24 y-o:* **71%** *25-34 y-o:* **69%** *35-44 y-o:* **68%** *45-54 y-o:* **53%** *Total:* **68%**	
Fabsitz et al, 1992	243	*20 y-o:* **82%** *25 y-o:* **78%** *40-50 y-o:* **73%** *42-56 y-o:* **73%**		
Martin (in Neale & Cardon, 1992)	3569	*18-30 y-o:* **80%** *+31 y-o:* **70%**	*18-30 y-o:* **78%** *+31 y-o:* 69%	
Meyer (in Neale & Cardon, 1992)	5588	**72%**	**75%**	
Allison et al, 1994	496	**93%** **91%**		
Carmichael & McGue, 1995	610 282 141			*18-38 y-o:* **82%** *39-59 y-o:* **70%** *60-81 y-o:* **63%**
Korkeila et al, 1995	5967		*18-54 y-o:* **64%** *24-60 y-o:* **67%**	
Herskind et al, 1996	1233	*46-59 y-o:* **46%** *60-79 y-o:* **61%**	46-59 y-o: **77%** *60-79 y-o:* **75%**	
Allison et al, 1996	53			*47-87 y-o:* **70%**
Hong et al, 1997	490			*50-85 y-o:* **30%**
Harris et al, 1995	1664	*18-25 y-o:* **71%**	*18-25 y-o:* **62%**	
Austin et al, 1997	315		*18-85 y-o:* ≈**80%** *Rate-of-change 10-y:* **56%**	
Kaprio et al, 2001	132	*50-76 y-o:* **28%**	*50-76 y-o:* **52%**	
Poulsen et al, 2001	303			*55-74 y-o:***80%**
Nelson et al, 2002	146	*22-88 y-o:* **89%**	*22-88 y-o:* **73%**	
Manck et al, 2003	785		46-62 y-o: 65%	

(Table continues in next page)

Author, year	N *	Heritability #		
		Men	Women	Overall
Schousboe et al, 2003	37.000	*20-29 y-o*: Australia: **67%** Denmark: **77%** Finland: **74%** Italy: **81%** Netherlands: **66%** Norway: 45% Sweden:**77%** UK: -- *30-39 y-o:* Australia: **75%** Denmark: **65%** Finland: **72%** Italy: -- Netherlands: **76%** Norway: **84%** Sweden: **73%** UK:--	*20-29 y-o:* Australia: **72%** Denmark: **73%** Finland: **78%** Italy: **85%** Netherlands: **81%** Norway:*74%* Sweden: **73%** UK: **75%** *30-39 y-o:* Australia: **73%** Denmark: **71%** Finland: **66%** Italy: -- Netherlands: **64%** Norway: **76%** Sweden: **75%** UK: **79%**	
Schousboe et al, 2004	624	*18–67 y-o:* **58%**	18–67 y-o: **63%**	
Cesari et al, 2007	60			*14–63 y-o:* **81%**
Souren et al, 2007	378			*18-34 y-o:* **85%**
Goode et al, 2007	495		*47±3 y-o:* **48%** *63±3 y-o:* **61%**	
Ordonana et al, 2007	662		*41-67 y-o:* **77%** Spain:	

* Number of twin pairs. # Heritability estimates are often reported for more than one phenotype and after various adjustments and restrictions in the different studies.

Longitudinal twin have shown variable results. For instance, among adult male twins, Stunkard and colleagues found a small increment in genetic effects on BMI from 77 to 84% in a 25-y follow-up (Stunkard et al., 1986a), while Fabsitz et al. showed a minor decrease from 82 to 73% in a 43-y follow-up, with genetic influences accounting for 70% of the increment in BMI during this period (Fabsitz et al., 1992, Fabsitz et al., 1994). On the other hand, longitudinal twin studies among women have reported overall stable genetic influences across time. For instance, Austin and colleagues found that genetic influences on BMI remained stable in a 10-year follow-up at around 80%, accounting for 57% of the change in the BMI during that period (Austin et al., 1997), while Korkeila et al. reported a relative stability in genetic influences on BMI in a 6-years follow-up (Korkeila et al., 1995).

Adoption studies also have compared the relative contribution of genetic influences with that of the shared / familial environment. Their results have highlighted the contribution of genetic influences on obesity by observing higher resemblance in adoptees with their biological parents than with their adoptive ones (Stunkard et al., 1986b, Price et al., 1987, Sorensen, 1989, Sorensen et al., 1989).

Family studies have provided further support for the existence of a strong genetic component in obesity. These studies have compared the relative

contribution of genetic influences with that of the shared / familial environment. By utilizing parent-offspring and sibling relationships (first-, second- or third-degree relatives), they offered heritability estimates of obesity related phenotypes. Most of the heritability estimates for BMI were between 35-50%. Longitudinal analyses also offered estimates for the change in BMI, and Rice et al. based on the Quebec family study found that 37% of changes in adult BMI in 12 years were accounted for by genetic influences, while Strug et al. based on the Framingham Heart Study, concluded that 45% of the increasing BMI across adult life was due to genetic effects (Rice et al., 1999a, Strug et al., 2004). All these estimates seemed somewhat lower than those obtained in studies of twins, although they concur that a substantial proportion of the variation in measures of obesity can be attributed to genetic factors (Tambs et al., 1992, Knuiman et al., 1996, Maes et al., 1997). Family studies proved valuable because they offer estimates of the genetic influences on obesity from populations other than twins. On the contrary, they were not fully conclusive, as they did not investigate for most possible sex-interactions within the phenotype (Lewis et al., 2005).

Association and linkage studies have offered relevant information on obesity genes with relatively small effects. Currently over 430 genes or chromosomal regions have been implicated in the etiology of obesity (Rankinen et al., 2006b). Phenotypic measures of obesity, such as BMI or body fat percentage, have shown positive association with different genes expressions, e.g. ApoB gene, ApoD gene, tumor necrosis factor alpha (TNF-α), dopamine receptor D2, low-density lipoprotein receptor (LDLR), leptin (LEP) and its receptor (LEPR), or the peroxisome proliferator-activated receptors (PPARs) alpha, beta or gamma (Rankinen et al., 2001). Similarly, BMI and other measures of obesity also have evidenced linkage for some other genes, such as the alkaline phosphatase 1 (ACP1), glucagon receptor (GLR), TNF-α or LEP (Chagnon et al., 2003).

Further segregation studies have revealed the existence of major obesity genes, their mode of inheritance and allele frequency. For BMI, for example, analyses have indicated that the genetic effects comprise both a major gene effect (accounting for 20-40% of the variability) and a complex polygenic component (accounting also for 20-40% of the variability) (Price et al., 1990, Province et al., 1990, Moll et al., 1991, Borecki et al., 1993, Ginsburg et al., 1998, Rice et al., 1999b, Colilla et al., 2000, Feitosa et al., 2000b). This observation seems consistent with other results in different populations and for other measures of obesity such as body fat mass (Rice et al., 1993, Comuzzie et al., 1995) or waist-hip ratio (Feitosa et al., 2000a). These major genes may include members of the leptin-melanocortin pathway, proinflamatory cytokines and uncoupling proteins (Rice et al., 1993, Comuzzie et al., 1995).

The patterns of inheritance of the major genes for obesity are still not well understood. While most of the studies indicated a recessive pattern of inheritance (Price et al., 1990, Province et al., 1990, Moll et al., 1991, Borecki et al., 1993), others suggested that their segregation would follow a codominant

manner (Cheng et al., 1998, Rice et al., 1999b, Colilla et al., 2000). These divergences between segregation analyses may arise as a result of different statistical procedures, differences between samples in *ethnic heterogeneity*, possible interactions with environmental factors (e.g. diet or physical activity) or the presence of *genetic epistasis* (gene-gene interactions) or *phenocopies* (obese persons due to other reasons than genetics).

In addition, genes affecting obesity-related phenotypes such as BMI are suggested to exert *pleitropic* effects on other associated phenotypes, e.g. systolic blood pressure (Cheng et al., 1998), energy expenditure (Feitosa et al., 2000b), insulin levels (Hong et al., 2000), diabetes and hypertension (Carmelli et al., 1994), or muscle characteristics and mobility (Tiainen et al., 2007). This provides potential explanation for the clustering of phenotypes observed in clinical and epidemiological data. However, evidences for those links are still limited, and while some studies have offered data on common genes for obesity and different metabolic diseases (Iwasaki et al., 2003, Stein et al., 2003), there is no knowledge about shared genetic influences between obesity and mobility phenotypes.

2.4 The association between high body fat and mobility

Clinical and epidemiological studies have shown a negative association between different measures of obesity (e.g. BMI or % of body fat) and mobility (e.g. walking speed or endurance), particularly among the older population (Pluijm et al., 2007). For example, the investigation by Launer and colleagues in the nationally representative US epidemiologic follow-up study National Health and Nutrition Examination Survey (NHANES) indicated that high BMI and body fat percentage are strong predictors of mobility limitations and disability in older women and men (Launer et al., 1994, Davison et al., 2002). Similarly, reports from the US Cardiovascular Health study and the Health and Body Composition study have consistently shown a negative association between body fat content and mobility performance (Visser et al., 1998, Visser et al., 2002a).

This negative association between obesity and mobility measures is considered multifactorial and its causes are still very much unknown. Firstly, it is possible that obesity causes mobility limitations. For example, obese people have excess body weight to carry, which may increase difficulties in moving by increasing the loading on the locomotor system, the overall energy expenditure and the metabolic demands for a given activity (Hulens et al., 2001, Hulens et al., 2003). Secondly, it is also possible that mobility disability increases body fat content. Persons with walking difficulties may be less active and as a result accumulate body fat. However, it is also possible that a third factor or factors cause both obesity and mobility limitations. For example, persons with poor

education and low socio-economic status tend to show both inferior mobility and higher obesity prevalence (Sainio et al., 2007).

An important pathway is the possible mediating role of common chronic conditions, such as type-2 diabetes, hypertension, osteoarthritis or cardio-vascular disease. Clark and Mungain indicated that among African-American women, the presence of arthritis, pain, and visual impairment contributed to mobility limitations (Clark et al., 1997). In recent analyses, Stenholm and colleagues explored the mediating role of these common chronic conditions in more than 3,000 adults and older Finnish men and women (Stenholm et al., 2007a). Their results indicated that the presence of co-morbidities explained 26-34% of the association between mobility and BMI in overweight and obese women, and 26-34% in men. In women, knee osteoarthritis contributed to the highest extent to the association (16-21%), followed by angina pectoris (7-11%). In men, diabetes (23-40%) and hypertension (13-15%) were the most important predictors.

As genetic influences also explain individual differences in obesity and walking ability, it is reasonable to assume that genetic factors may mediate this association. Data from animal models have offered consistent support to the hypothesis that common genes influence obesity and mobility. For example, Wisloff and colleagues reported that in a group of rats genetically selected for poorer mobility and reduced endurance capacity body weight consistently increased (Wisloff et al., 2005). In that study, the occurrence of high adiposity with genetic selection for low mobility was preceded by metabolic changes that led to high blood pressure, hyperinsulemia or increased blood triglyceride concentration. Despite the evidences in animals, there is no precise knowledge on the extent of a shared genetic background between obesity and mobility in humans. Therefore, it is important to identify the possible genetic link underlying the association between mobility and obesity in humans.

3 AIMS OF THE STUDY

This thesis was intended to investigate the genetic and environmental influences on the cross-sectional and longitudinal association between obesity and mobility in older women. Consequently, the specific aims were:

1. To investigate the extent to which genetic and environmental influences underlie changes in women's body composition from middle to old age

2. To ascertain how much genetic and environmental influences account crossectionally and longitudinally for walking ability in older women

3. To examine whether common genetic influences explain the association between mobility and body fat content in older women

4. To determine the extent to which the genetics of weight gain and obesity across adulthood may underlie and impact the mobility level in aging

4 PARTICIPANTS AND METHODS

4.1 Participants

4.1.1 Recruitment

The present study is part of the Finnish Twin Study on Aging (FITSA). The study sample was recruited among the participants in The Finnish Twin Cohort Study, which comprises all the same-sex twin pairs born before 1958 and in which both co-twins were alive in 1975 (n=13 888 twin pairs) (Kaprio et al., 2002). Initially, the zygosity of the participating twin pairs in the Finnish Twin Cohort study were determined as monozygotic (MZ), dizygotic (DZ) or undetermined zygosity (XZ) twins in 1975, using a validated questionnaire (Kaprio et al. 1978, Sarna et al. 1978) in which both twins answered questions about their similarity of appearance in childhood. In the Finnish Twin Cohort there were 1260 female twin pairs born between 1924 and 1937. In this group, an invitation to participate in FITSA was sent to every MZ (n=178 pairs) and every third DZ (n=212 pairs) and to all XZ (n=24 pairs) twins. Altogether, they were 414 female pairs aged 63 to 76 years old surviving in 2000. To be included, 3 main criteria were followed: both twin pair members had to agree to take part, they should be able walk 2 km and also to travel independently to the research center. The reasons for nonparticipation were that one or both sisters were unwilling to take part (106 pairs), had poor health status (85 pairs) or had died after vital status was last updated for all cohort members (6 pairs). Eventually, 98 MZ, 106 DZ and 13 XZ twin pairs comprised the sample in 2001. Later on, the zygosity of the participants was confirmed using a battery of ten highly polymorphic gene markers, at the National Public Health Institute in Helsinki, Finland. As a result of all procedures, the study group in the FITSA baseline evaluations consisted of 217 twin-sister pairs, including 103 MZ and 114 DZ pairs.

In 2004, an invitation to take part in a 3-year follow-up examination was sent to all baseline participants. However, 8 of the individuals refused to participate due to the poor health status, 7 individuals had died and 106

individuals consented to participate solely in an interview. Thus, the FITSA follow-up sample consisted of 149 MZ and 164 DZ individuals, who participated in the laboratory measurements in addition to the interview.

The ethics committee of the Central Hospital of Central Finland approved the FITSA study protocol. Each participant signed a written informed consent.

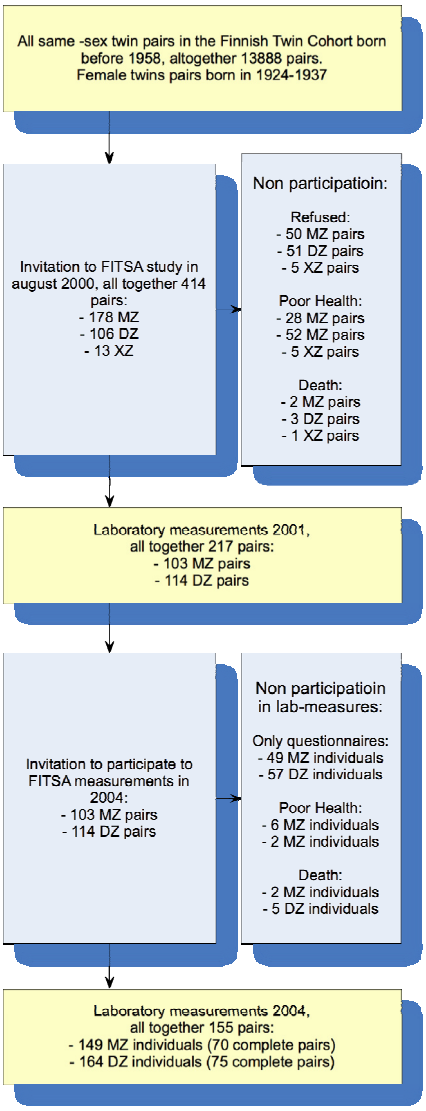


FIGURE 2 Recruitment of the participants in FITSA (years 2001 and 2004)

4.1.2 Measurements

Similar measurement protocols were used in 2001 and in the 2004 follow-up. The day prior to testing, the participants arrived from all over Finland at the

city of Jyväskylä, where they stayed overnight at a hotel. All subjects were requested to avoid exercise or sauna within 12 hours of the laboratory measurements, as well as to refrain from alcohol intake for 24 hours.

The following day, the twin sisters attended the laboratory tests together. The complete procedures and stay at the laboratory facilities lasted approximately 5 hours per participant. During the tests, every person was evaluated alone and blinded to her sister's results.

A. Health ascertainment and medication

First, in the early morning their general health status was checked during a clinical examination, in which, for example, information on chronic conditions, symptoms, blood pressure, medication and health-related habits was recorded (e.g. smoking, physical activity and walking, alcohol intake or other habits). Cardiovascular, musculoskeletal and neuromuscular conditions, in particular, were evaluated and attention was paid to risk factors and contraindications for the exercise and functional performance measurements.

B. Evaluation of body size and body mass index (BMI) (studies 3 and 5)

During the medical examination in 2001 and 2004, participants' body weight (to the nearest 0.1 kg) and height (to the closest 0.5 cm) were measured in light indoor clothing without shoes using a calibrated beam-balance and a medical stadiometer, respectively. Based on these records, their corresponding BMI value was later computed as weight (kg) divided by the squared height (m^2).

Data on the weight and height of the participants in FITSA was collected in addition from available records in the Finnish Twin Cohort study in the years 1975, 1981 and 1990. Information on those earlier occasions was gathered using a standardized questionnaire. The validity and reliability of the questionnaire was controlled in a relatively large sub-sample of twin sisters, by contrasting self-reported weight and height with measures taken in a clinical examination after the questionnaire. The correlation between self-reported and clinically assessed body dimensions was over 0.90, suggesting a good reliability of the self-reported BMI (Korkeila et al., 1998, Silventoinen et al., 2000). A more detailed description of the measurement protocol used in the Finnish Twin Cohort study is published elsewhere (Silventoinen et al., 2004).

As a result of all the above procedures, the data on the participants' BMI allowed the prospective study of 5 waves of observations from 1975, to 2004 in a total 29-year follow-up. Table 3 shows a description of the final numbers of individuals and complete pairs with available data on BMI in every occasion.

C. Evaluation of body fat percentage (study 4)

Body composition was measured using bioelectrical impedance testing using a 4-terminal bioelectrical impedance analyzer (RJL Spectrum Bioelectrical

Impedance, BIA 101/SC Akern, RJL-System) (Deurenberg et al., 1990) according to the manufacturer's recommendations. Measurements were conducted for all participants during the clinical examination in 2001 and 2004, before any other tests and more than 2 hours after the participant's last meal. During the measurements, participants were instructed to lie down in a supine position on a medical examination table, with arms at 30° from the body and the legs not touching each other. Detecting electrodes were placed on an imaginary line bisecting the ulnar head of the right hand and on the medial malleolus of the right foot, while signal electrodes were placed on the first middle joint of the right finger and on the base of the second toe of the right foot. Body composition software was later utilized to calculate the percentage of body fat mass with appropriate equations using the obtained resistance and reactance values along with participant's gender, age, height, and weight.

D. Evaluation of walking speed (studies 1, 2, and 4)

Maximal walking speed over 10 meters (Aniansson et al., 1980) was measured using a validated method (Wolf et al., 1999) in the laboratory corridor during the examinations in 2001 and 2004. Every person was asked "to walk as fast as possible, without compromising safety". For security reasons, 2 persons used a cane. To minimize the effects of acceleration and deceleration, measurements were taken over the middle 10 meters of a longer walkway where 3 meters before the start were allowed for acceleration. Time was recorded by photocell devices. The best performance out of two trials was taken as the final outcome. The coefficient of variation in the maximal walking speed test in the present study was 5% (Pajala et al. 2005).

E. Evaluation of walking endurance (Studies 1, 2, 4 and 5)

Walking endurance was assessed using a validated six-minute walking test ("ATS statement: guidelines for the six-minute walk test," 2002) during the laboratory examination in 2001 and 2004. The subjects were requested to walk back and forth along a 50m indoor straight track for six minutes and to complete as many laps as possible. The standardized protocol and security conditions followed the American Thoracic Society Statement ("ATS statement: guidelines for the six-minute walk test," 2002). The distance covered by the end of the six minutes was recorded as the outcome. The reliability of this test in healthy elderly persons is considered very high (e.g. intra-class correlation = 0.93) (Magan et al., 1994).

4.1.3 Final number of persons in the sample

The number of individuals who participated in FITSA with available information on weight and height in the years 1975, 1981 and 1990 (waves 1 to 3) may be seen in table 4 and in the ***Results*** section.

In 2001 (wave 4), the study group consisted of 103 monozygotic (MZ) and 114 dizygotic (DZ) intact twin pairs. Data on body weight, height and body fat percentage was available from all of them. However, the test of maximal walking speed was performed by 199 MZ and 219 DZ individuals, while the test of walking endurance by 170 MZ and 189 DZ individuals.

In 2004 (wave 5), the total sample consisted of 149 MZ and 164 DZ individuals at the start. All of them had data on body weight, height and body fat percentage, while only 142 MZ and 154 DZ individuals had data on walking speed, and 103 MZ and 110 DZ individuals also on walking endurance.

TABLE 3 Variables entered into the study, with total numbers of twin sisters considered at every wave.

	Wave 1	**Wave 2**	**Wave 3**	**Wave 4**	**Wave 5**
Year	1975	1981	1990	2001	2004
Variables	Self-rated - Weight - Height - BMI	Self-rated - Weight - Height - BMI	Self-rated - Weight - Height - BMI	Lab-measured - Weight - Height - BMI - Body fat % - 10-m Walking speed - 6-min Walking endurance - Walked Km/week	Lab-measured - Weight - Height - BMI - Body fat % - 10-m Walking speed - 6-min Walking endurance - Walked Km/week
Total N persons	414	396	254	434	313
MZ / DZ	193 MZ / 221 DZ	190 MZ / 206 DZ	120 MZ / 134 DZ	206 MZ / 228 DZ	149 MZ / 164 DZ

4.2 Statistical Methods

4.2.1 Descriptive statistics

In all 5 studies, the descriptive statistics were obtained using SPSS (SPSS, 2003), Stata (StataCorp, 2005) and Mx (Neale, 1997) software packages. The normality of the data was tested by the Kolgomorov-Smirnoff test, equality of means and variances by ANOVA and t-test for repeated measures using SPSS and STATA software, which allows controlling for the clustering of possibly correlated observations from twin pairs. To obtain preliminary information on the patterns of relations between MZ and DZ pairs for every phenotype, we examined within-pair resemblances by computing intraclass correlation coefficients (ICCs) in SPSS. Correlations between traits were calculated using MX software.

In **Study 5**, the relations between body mass index at every wave of measurement and mobility in 2001 and 2004 were analyzed by computing age- and baseline BMI- adjusted linear regression models for complex samples on STATA software, which allows for control of clustering of possibly correlated observations from twin pairs.

4.2.2 Biometric statistics

The first step was to estimate genetic and environmental influences on every single phenotype using univariate genetic analyses. Subsequently, 3 different multivariate analyses were conducted.

A. Cholesky decomposition model (Studies 1 and 2)

In Cholesky decompositions, genetic and environmental influences on a given trait are modeled to be shared by a second trait. Therefore, in **Study 1** a Cholesky decomposition was fitted to investigate whether common genetic and environmental influences explained the association between walking speed and endurance phenotypes.

In **Study 2**, two Cholesky decompositions were also modeled for walking speed and endurance phenotypes respectively, in order to estimate whether influences identified in 2001 (wave 4) remained present also at the 2004 follow-up (wave 5).

To improve the sample size in **Studies 1** and **2** in which the Cholesky decomposition were calculated, data was statistically imputed in the walking endurance variable, for those cases where data existed for both sisters on walking speed and was missing for one sister for the walking endurance test. These procedures were done using the Markov Chain Monte Carlo (MCMC) simulation technique using SAS 8.2, for MZ and DZ twins separately. That was done to avoid possible bias in the imputation of values due to differences in resemblance because of the zygosity of the twins. The imputation took into account information on the individual's walking speed result, her sister's speed and endurance test results, and the age of the twin pair (SAS Institute, 2001, Pedersen et al., 2003).

At wave 4, 15 MZ and 22 DZ were imputed. The final number of complete pairs that entered into the Cholesky model for the study 2 was 92 MZ and 105 DZ with full information on both walking speed and endurance.

Following a similar procedure, values in walking endurance were also imputed at wave 5 for 16 MZ and 25 DZ. The final number of pairs with complete data at wave 4 and 5 entering into the analyses for **Study 2** was 63 MZ and 67 DZ pairs on walking speed, and 56 MZ and 58 DZ on walking endurance.

B. Independent pathway model (Study 4)

In this type of modeling, it is hypothesized that there are cross-trait as well as trait-specific genetic and environmental effects on a number of observed phenotypes. Thus a trivariate independent pathway model was fitted to the raw data in **Study 4**, (including observed and missing data), to estimate shared (cross-trait) genetic and environmental influences between body fat percentage, walking speed and endurance, as well as non-shared (trait-specific) effects on them.

C. Latent growth models (Studies 3 and 5)

Latent growth modelling is a statistical technique based on structural equation modelling (SEM). It is a longitudinal analysis technique to estimate growth (or slope) over a period of time. It is widely used in the field of behavioural science, education and social science, and it is also called latent growth curve analysis.

When data is available from various waves of observations across different moments, the biometric growth modelling provides estimates for genetic and environmental influences arising from two possible latent sources: a "Level" or stable component which remains largely unchanged through the study period, and a "Slope" component representing the rate of change between waves of observations. The slope component in a variable (either positive or negative) is modelled in the form of the relationship between the observed variables (e.g., the same variable measured repeatedly over time) and latent variables. An observed variable is a measured variable, such as weight, height, or BMI, while the "latent" attribute means that it is not directly observable but is statistically estimated through one or more observed variables (Park et al., 2005).

Level and Slope effects are considered general components and they contribute to the variance at all waves of assessment. These two general components are allowed to covary. However, while Level effects are considered stable across every wave of measurements, Slope effects have different loadings across waves and therefore these loadings must be specified in the model.
In the present study, a linear component of change was modelled. In addition to general components, wave-specific effects were also estimated, which reflect genetic or environmental (and measurement error) variances at a given time in life not explained by longitudinal components. Owing to the nature of wave-specific effects, they are not allowed to covary across waves.

Before the modelling, BMI data was statistically transformed using power transformation methods (power 1/3) to avoid high skewness and kurtosis at some follow-ups that could compromise the genetic modelling.

In **Study 3**, latent growth models were fitted to the raw data to estimate genetic and environmental influences on the level and rate of change in BMI from middle to old age (in a 29-year follow-up). In **Study 5**, a new latent component was introduced in the initial growth-modeling procedures accounting for the stable component (*Level)* of walking endurance in the last 3 years of the study period, and using the information on this phenotype from waves 4 and 5 of the study. As a result we built and tested a complex growth model with 7 phenotypes (5 waves of BMI and 2 waves of Mobility).

To avoid biased estimates due to age differences in the sample or different follow-up interludes, growth model analyses in the present data were adapted. Firstly, to control the effect of age differences between twin pairs, individuals' age was introduced into the modelling process as a definition variable. In addition, as the waves of observations were collected at uneven intervals of time, the loadings from the Slope component in the model needed to be adjusted. Thus, while the loadings from the Level component were fixed to 1,

the respective loadings from the Slope component were 0 (or no growth), 1, 2.5, 4.33 and 4.83. These values are expressed as units of times of 6 years for the known intervals of 6, 15, 26 and 29 years from wave 1.

4.2.3 The model fitting

All models estimated were fitted to the raw data with MX software (Neale, 1997) by using maximum likelihood algorithms and treating unobserved data as missing-at-random (Little et al., 1987). This approach corrects the likelihood of the model for missing data and usually offers more accurate estimates of parameters than standard analyses in which pairs are deleted due to missing data (Greenland et al., 1995). The significance of estimates and path coefficients were tested by removing them sequentially in different subsequent models. Their fit was compared against the fit of the unconstrained initial model in which a higher number of possible paths of relations and estimates were present. This comparison was done by applying likelihood-ratio tests (Neale et al., 2000). Likelihood-ratio tests are based on the deviance variation (-2ln(L) and degrees of freedom) between an initial, unconstrained / less-constrained model and a candidate, hypothetical model. In the case where the likelihood of the hypothetical sub-model is statistically different ($p \leq 0.05$) from than of the initial model, the fit of the sub-model is poorer and it may be rejected.

In **Studies 3, 4** and **5**, where models were more complex and included measures of obesity and walking, the fitting process was supplemented with the Akaike's Information Criterion (AIC) (Akaike, 1987) and the Schwartz's Bayesian Information Criterion (BIC) (Schwartz, 1978). Because the likelihood-ratio tests tend to favor models with a larger number of estimated parameters, the AIC was calculated as it disfavors models with more parameters and so balances model fit with model parsimony. Its use is recommended in large models with a high number of observations, where minor deviations may result in differences in the likelihood-ratio (Christensen et al., 2003). Similarly, the BIC disfavors models with a larger number of estimated parameters, but it also takes into account sample size, which may be particularly important in longitudinal, very complex models with varying numbers of observations. Smaller values of AIC and BIC indicate a better fit to the data.

5 RESULTS

5.1 Overall sample description

Table 4 show means (and confidence intervals) for all the characteristics of the participants at any of the 5 waves of measurements, from 1975 to 2004. Data showed no significant differences between MZ and DZ twins in mean values for body height, weight, BMI, body fat percentage, walking speed over 10 meters or distance covered in the 6-minute walk.

Participants' age, body mass index (BMI), body fat percentage and habitual walking per week were significantly associated with both walking traits ($p<0.01$). That is, older, more obese twins had poorer walking results in both the 2001 and the 2004 data.

TABLE 4 Sample characteristics and results at every wave of measurements (no data imputed). Means, 95% confidence intervals (95% CI) and pair-wise correlations (ICCs) are also shown

	WAVE 1: year 1975			WAVE 2: year 1981			WAVE 3: year 1990			WAVE 4: year 2001			WAVE 5: year 2004		
Variable	**N ***	**Mean (95% CI)**	**ICC (95% CI)**	**N ***	**Mean (95% CI)**	**ICC (95% CI)**	**N ***	**Mean (95% CI)**	**ICC (95% CI)**	**N ***	**Mean (95% CI)**	**ICC (95% CI)**	**N ***	**Mean (95% CI)**	**ICC (95% CI)**
Age (years)	414/200	42.6 (42.3-42.9)		396/190	48.6 (48.3-49.0)		254/118	55.7 (55.4-56.0)		434/217	68.6 (68.3-69.0)		313/145	71.1 (69.7-71.4)	
- MZ twins	193/92	42.3 (41.8-42.8)	1.00 (--)	190/89	48.4 (47.8-48.9)	1.00 (--)	120/56	55.3 (54.9-55.8)	1.00 (--)	206/103	68.3 (67.8-68.9)	1.00 (--)	149/70	70.5 (69.9-71.1)	1.00 (--)
- DZ twins	221/108	42.9 (42.5-43.3)	1.00 (--)	206/101	48.9 (48.4-49.3)	1.00 (--)	134/62	56.0 (55.7-56.3)	1.00 (--)	228/114	68.9 (68.3-69.0)	1.00 (--)	164/75	71.6 (71.1-72.0)	1.00 (--)
Weight (kg)	414/200	62.2 (61.8-63.5)		396/190	64.2 (63.3-65.1)		254/118	66.9 (65.6-68.3)		434/217	70.1 (68.9-71.2)		313/145	70.0 (67.9-71.0)	
- MZ twins	193/92	62.2 (61.0-63.3)	0.63 (0.49-0.74)	190/89	63.8 (62.5-65.1)	0.57 (0.41-0.70)	120/56	66.3 (64.4-68.2)	0.91 (0.85-0.94)	206/103	69.6 (68.0-71.2)	0.65 (0.52-0.75)	149/70	69.0 (66.2-70.9)	0.70 (0.56-0.80)
- DZ twins	221/108	63.0 (62.0-64.2)	0.32 (0.14-0.48)	206/101	64.6 (63.3-65.9)	0.30 (0.12-0.47)	134/62	67.5 (65.6-69.4)	0.43 (0.20-0.61)	228/114	70.6 (69.0-72.2)	0.41 (0.25-0.55)	164/75	70.4 (68.4-72.4)	0.42 (0.22-0.60)
Height (m)	414/200	1.61 (1.60-1.62)		396/190	1.61 (1.60-1.62)		254/118	1.60 (1.60-1.62)		434/217	1.58 (1.57-1.59)		313/145	1.57 (1.57-1.58)	
- MZ twins	193/92	1.61 (1.60-1.62)	0.92 (0.88-0.95)	190/89	1.61 (1.60-1.61)	0.88 (0.82-0.91)	120/56	1.60 (1.60-1.61)	0.74 (0.59-0.84)	206/103	1.58 (1.57-1.59)	0.94 (0.92-0.96)	149/70	1.57 (1.56-1.58)	0.94 (0.91-0.97)
- DZ twins	221/108	1.62 (1.61-1.62)	0.50 (0.34-0.63)	206/101	1.62 (1.61-1.62)	0.48 (0.31-0.62)	134/62	1.61 (1.60-1.62)	0.40 (0.17-0.59)	228/114	1.59 (1.58-1.60)	0.56 (0.41-0.67)	164/75	1.58 (1.57-1.59)	0.53 (0.34-0.67)
BMI (kg/m^2)	414/200	23.9 (23.5-24.3)		396/190	24.6 (24.3-26.2)		254/118	25.7 (25.2-26.2)		434/217	28.0 (27.5-28.4)		313/145	28.2 (27.5-28.7)	
- MZ twins	193/92	23.9 (23.5-24.4)	0.57 (0.40-0.68)	190/89	24.6 (24.1-25.0)	0.59 (0.43-0.71)	120/56	25.4 (24.7-26.1)	0.74 (0.56-0.84)	206/103	28.0 (27.3-28.7)	0.62 (0.48-0.72)	149/70	28.0 (27.1-28.8)	0.74 (0.61-0.83)
- DZ twins	221/108	24.1 (23.7-24.3)	0.29 (0.11-0.46)	206/101	24.7 (24.2-25.2)	0.29 (0.10-0.46)	134/62	25.9 (25.2-26.6)	0.39 (0.15-0.58)	228/114	28.0 (27.3-28.6)	0.41 (0.25-0.55)	164/75	28.3 (27.5-29.1)	0.44 (0.24-0.60)
Body fat percentage	-	-	-	-	-	-	-	-	-	434/217	33.4 (32.2-34.3)		313/145	33.5 (32.7-34.2)	
- MZ twins	-	-	-	-	-	-	-	-	-	206/103	33.3 (32.2-34.3)	0.67 (0.55-0.77)	149/70	33.1 (31.9-34.2)	0.83 (0.74-0.89)
- DZ twins	-	-	-	-	-	-	-	-	-	228/114	33.6 (32.7-34.4)	0.23 (0.05-0.40)	164/75	33.8 (32.7-34.2)	0.47 (0.27-0.63)
10 m walking speed	-	-	-	-	-	-	-	-	-	418/206	1.72 (1.69-1.80)		290/130	1.79 (1.70-1.80)	
- MZ twins	-	-	-	-	-	-	-	-	-	199/98	1.75 (1.69-1.80)	0.62 (0.48-0.73)	140/63	1.79 (1.71-1.85)	0.69 (0.54-0.80)
- DZ twins	-	-	-	-	-	-	-	-	-	219/108	1.71 (1.70-1.77)	0.47 0.31-0.61)	150/67	1.77 (1.67-1.81)	0.48 (0.28-0.64)
6-min walking test (m)	-	-	-	-	-	-	-	-	-	396/197	525.4 (517.8-533.1)		217/118	519.0 (508.8-529.3)	
- MZ twins	-	-	-	-	-	-	-	-	-	185/92	521.7 (509.3-534.1)	0.52 (0.35-0.65)	114/57	524.0 (508.0-540.0)	0.66 (0.48-0.78)
- DZ twins	-	-	-	-	-	-	-	-	-	211/105	528.7 (519.3-538.1)	0.36 (0.18-0.51)	122/61	514.5 (501.2-527.8)	0.36 (0.13-0.56)
Habitual walking (km/week)	-	-	-	-	-	-	-	-	-	410/213	11.5 (10.8-13.5)		301/139	10.8 (9.8-11.9)	
- MZ twins	-	-	-	-	-	-	-	-	-	203/100	12.1 (10.8-13.4)	0.58 (0.43-0.70)	145/68	12.1 (10.5-13.9)	0.60 (0.42-0.73)
- DZ twins	-	-	-	-	-	-	-	-	-	227/113	10.9 (9.7-12.1)	0.27 (0.09-0.43)	156/71	9.5 (8.3-10.8)	0.11 (-0.12-0.33)

*N expressed as number of individuals / complete twin pair

5.2 Study 1: the genetic and environmental relation between walking speed and endurance

The cross-sectional analyses of walking speed and endurance were done using tests results from 92 MZ and 105 DZ twin sisters with both walking speed and endurance. The mean age of the MZ pairs was slightly lower than that of the DZ pairs, and age correlated with the measures of walking speed and endurance in the total study sample ($p<0.001$).

The comparison of the ICCs for walking speed ($r_{mz}=0.55$; $r_{dz}=0.45$) and endurance ($r_{mz}=0.51$; $r_{dz}=0.31$) suggested the presence of additive genetic effects in both phenotypes. Preliminary univariate modelling confirmed that A, C and E were present for walking speed and endurance. In a subsequent bivariate Cholesky decomposition, it was found that the model with A, C and E was the most parsimonious and theoretically acceptable. This bivariate ACE model showed an overlap of genetic influences ($r_g=1.00$) on the walking phenotypes that explained 16% (95% CI, 00%-54%) of the variance in maximal walking speed and 20% (95% CI, 00%-56%) in walking endurance. The rest of the influences on each phenotype were explained by C and E, which were partially shared by both phenotypes. The correlation between the common and specific environmental factors were r_c = 0.74 (95% CI, –1.00 to 1.00) and r_e = 0.63 (95% CI, 0.53-0.70), respectively.

5.3 Study 2: the stability and change in the genetic influences on mobility in old women

Among those complete pairs with walking data at wave 4 and 5, the average walking speed did not change from baseline (1.8 ± 0.3 m/s) to follow-up (1.8 ± 0.4 m/s). However, their walking endurance declined 12.1 ± 63.8 m ($p<0.001$) from the baseline (531.7 ± 75.9 m) to the follow-up (520.8 ± 83.4 m), as did also their walking habits (average decline: 1.1±7.5 km/week) with 9.2% less km ($p=0.030$) within a normal week.

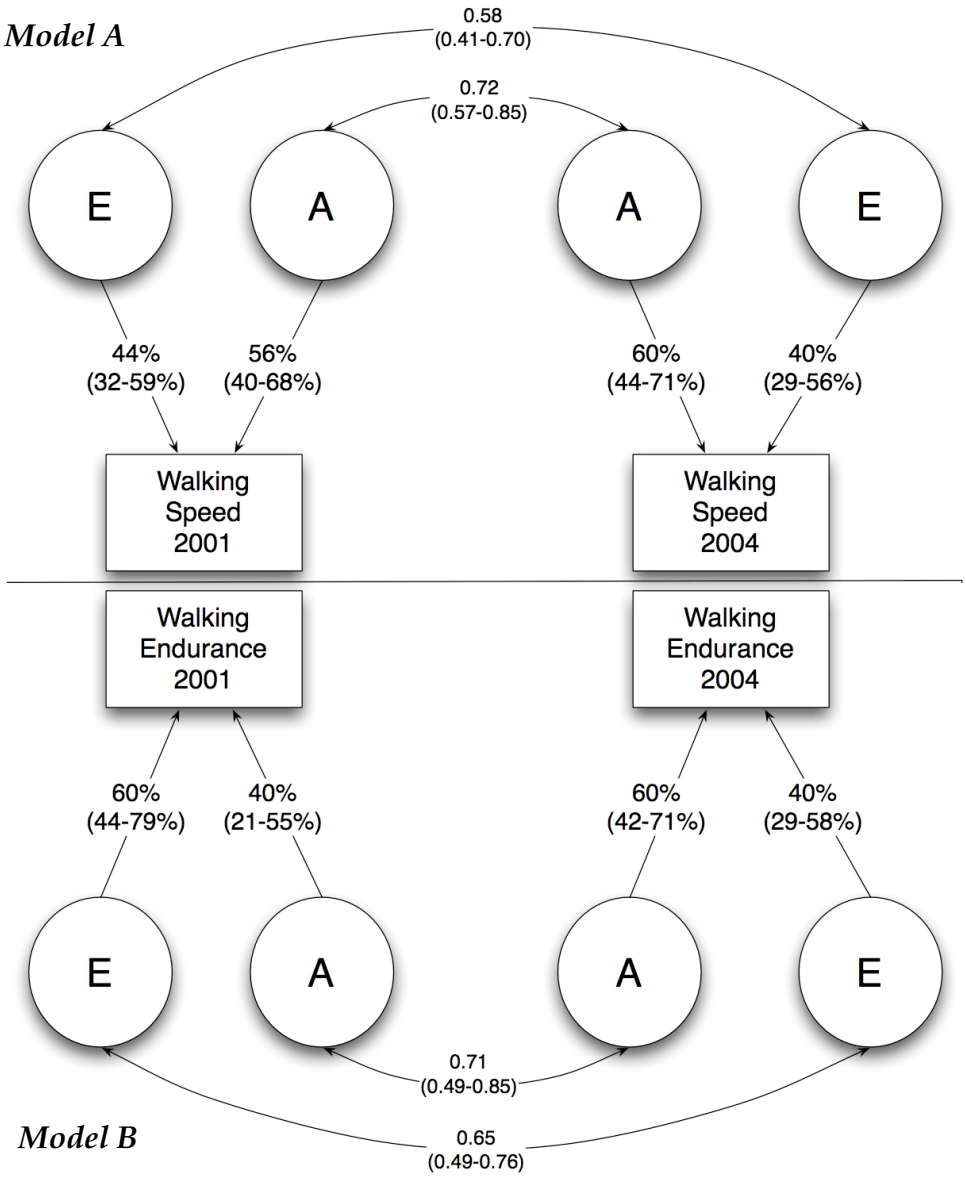
TABLE 5 Characteristics and tests results (overall and by zygosity) for pairs with data at both baseline and follow-up at every wave of measurements (with data imputed by statistical methods). Means, 95% confidence intervals (95% CI) and pairwise correlations (ICC) are also shown

	Results for twin pairs with walking data at both years 2001 and 2004					Results for dropping-out pairs		
	Wave 4: Year 2001			Wave 5: year 2004		Wave 4: Year 2001		
Variable	**N**	**Mean (95% CI)**	**ICC (95% CI)**	**Mean (95% CI)**	**ICC (95% CI)**	**N**	**Mean (95% CI)**	**ICC (95% CI)**
Age (years)	260	68.1 (67.7-68.4)		70.1 (69.7-71.4)		152	69.3 (68.7-70.0)	
- MZ twins	126	67.5 (66.9-68.1)	1.00 (--)	70.5 (69.9-71.1)	1.00 (--)	70	69.3 (68.3-70.2)	1.00 (--)
- DZ twins	134	68.6 (68.1-69.5)	1.00 (--)	71.6 (71.1-72.0)	1.00 (--)	82	69.3 (68.6-70.1)	1.00 (--)
BMI (kg/m²)	260	27.9 (27.3-28.5)		28.0 (27.4-28.7)		152	27.8 (27.1-28.5)	
- MZ twins	126	27.8 (26.9-28.7)	0.64 (0.46-0.76)	27.7 (26.8-28.7)	0.74 (0.60-0.83)	70	28.2 (27.2-29.1)	0.67 (0.44-0.82)
- DZ twins	134	28.1 (27.3-28.8)	0.41 (0.19-0.59)	28.3 (27.5-29.1)	0.47 (0.28-0.64)	82	27.5 (26.4-28.6)	0.52 (0.25-0.71)
Habitual walking (Km/week)	260	12.5 (11.2-13.8)		11.4 (10.1-12.7)		152	10.7 (9.5-12.0)	
- MZ twins	126	14.0 (12.2-15.9)	0.60 (0.41-0.74)	12.8 (11.0-14.8)	0.55 (0.35-0.70)	70	10.0 (8.1-11.8)	0.34 (0.01-0.60)
- DZ twins	134	11.0 (9.3-12.7)	0.27 (0.03-0.48)	9.8 (8.4-11.4)	0.16 (-0.08-0.38)	82	11.3 (9.7-13.0)	0.18 (-0.13-0.46)
Walking Speed (m/s)	260	1.8 (1.7-1.8)		1.8 (1.7-1.8)		152	1.7 (1.6-1.7)	
- MZ twins	126	1.8 (1.7-1.8)	0.60 (0.41-0.73)	1.8 (1.8-1.9)	0.65 (0.47-0.77)	70	1.7 (1.6-1.8)	0.64 (0.40-0.80)
- DZ twins	134	1.8 (1.7-1.8)	0.49 (0.28-0.65)	1.7 (1.7-1.8)	0.43 (0.22-0.61)	82	1.7 (1.6-1.7)	0.45 (0.17-0.66)
Walking Endurance (m)	228	531.7 (522.3-541.1)		520.8 (509.9-531.4)		166	515.8 (504.3-527.3)	
- MZ twins	112	529.4 (515.0-544.1)	0.42 (0.18-0.62)	525.6 (509.1-541.9)	0.66 (0.48-0.78)	72	509.3 (488.5-530.0)	0.64 (0.39-0.79)
- DZ twins	116	533.6 (521.2-546.1)	0.37 (0.13-0.57)	516.1 (501.6-530.7)	0.36 (0.11-0.56)	94	520.8 (508.0-534.8)	0.32 (0.04-0.55)

As in the overall sample, among those pairs age, body mass index (BMI) and habitual walking per week were significantly associated with both walking traits ($p<0.01$); that is, older, more obese, and less active twins had poorer walking results in both the 2001 and the 2004 data.

The bivariate Cholesky decompositions for walking speed and endurance independently indicated that the most parsimonious model showing a satisfactory fit with the data and providing a theoretically acceptable answer to the study problem contained additive genetic (A) and specific environmental influences (E) at baseline and follow-up.

Walking speed (Figure 3, Model A) showed parallel additive genetic influences at baseline (56%; 95%CI: 40-68%) and follow-up (60%; 95%CI: 44-71%). Most of the genetic influences at baseline were still present at follow-up (r_g=0.72; 95%CI: 0.57-0.85).



Note: A and E refer to additive genetic and specific environmental influences, respectively. Estimates for each pathway to the walking speed and endurance phenotype are shown (with 95% confidence intervals, 95%CI). Additive genetic and specific environmental correlations between baseline and follow-up results (rg and re) are also shown as curved arrows, along with their estimates (and 95%CI).

FIGURE 3 Summary models of the changes over 3 years in the influences on walking speed (Model A) and endurance (Model B)

Similarly, specific environmental influences on walking speed remained stable from baseline (44%, 95%CI: 32-59%) to follow-up (40%, 95%CI: 29-56%), with baseline environmental influences largely present also at follow-up (r_e=0.58,

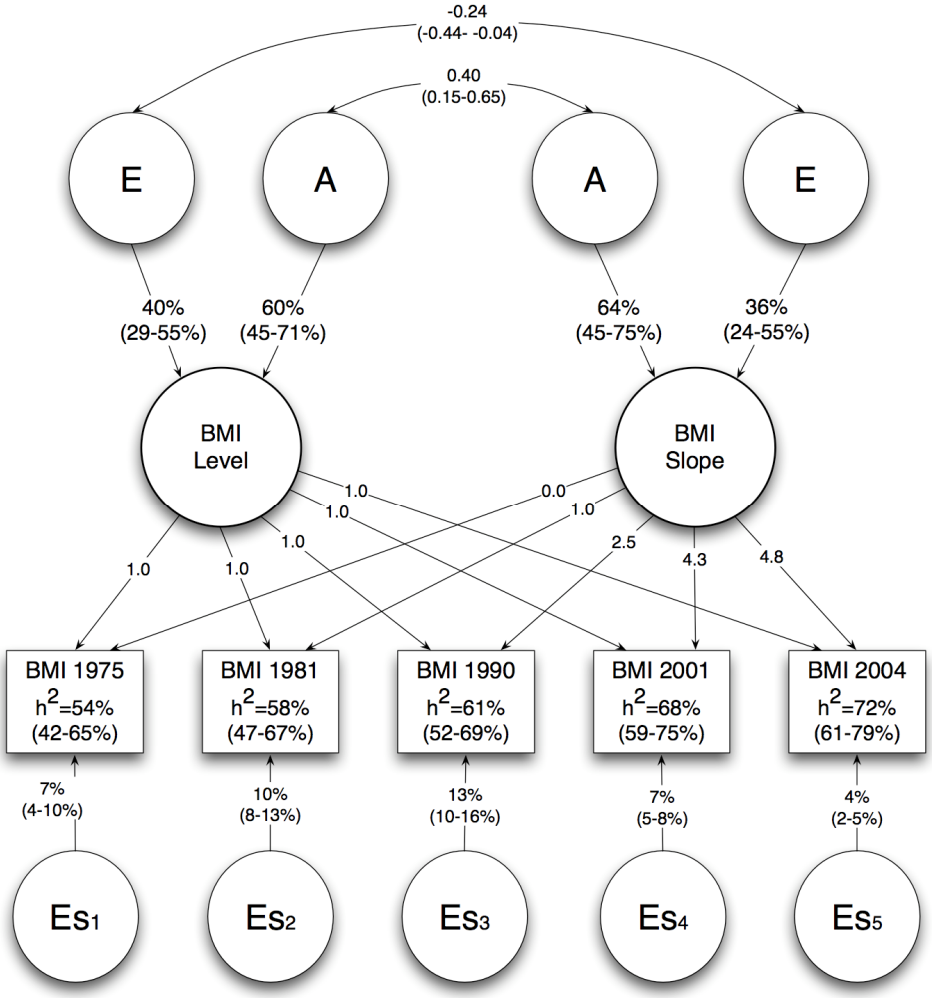
95%CI: 0.41-0.71). Walking endurance (Figure 3, Model B) showed additive genetic influences at baseline (40%; 95%CI: 21-55%) that increased at follow-up (60%; 95%CI: 42-71%). Most of the genetic influences found at baseline were later present at follow-up (r_g=0.71; 95%CI: 0.49-0.86). Specific environmental influences on walking endurance decreased from baseline (60%, 95%CI: 44-79%) to follow-up (40%, 95%CI: 29-58%), with baseline environmental influences remaining at follow-up (r_e=0.65, 95%CI: 0.49-0.76). Total phenotypic and genetic variances (v_g and $v_{p)}$ in both walking speed and endurance increased from baseline (speed: v_{p1}=0.09, v_{g1}=0.05; endurance: v_{p1}=15.8, v_{g1}=6.26) to follow-up (speed: v_{p2}=0.14, v_{g2}=0.08; endurance: v_{p2}=17.30 v_{g2}=10.12). However, while the specific environmental variance (v_e) increased for walking speed (v_{e1}=0.04, v_{e2}=0.06), it decreased for walking endurance (v_{e1}=9.54, v_{e2}=7.16).

5.4 Study 3: the genetics of the longitudinal evolution of BMI

Mean BMI increased during the study period from 24.9 (95%CI: 23.5-24.3) kg/m^2 at mean age 43, to 28.8 (95%CI: 27.5-28.7) kg/m^2 at mean age 71, thus representing a total average increment of 17% (95%CI: 15.4-18.4%) of the baseline value. An overall gain in relative weight was observed in about 92% of all participants. The variance in BMI also increased steadily from 9.7 at the baseline to 25.7 at the end of the study ($p<0.001$). At the baseline, only 4.4% of the participants were obese (BMI >30 kg/m^2), while at wave 4 that percentage had increased to 28.1% and at wave 5 to 31.4%. The women who were initially obese did not decrease in weight with age. The small proportion of women whose BMI decreased or remained stable had normal or at most moderately above normal weight at baseline.

The analyses of the pair-wise correlations in BMI (table 4) showed that MZ twins resembled each other more than DZ twins, suggesting the presence of additive genetic influences at all waves of measurements. Fitting a preliminary Cholesky decomposition for BMI using each of the 5 waves of observations confirmed that sub-models without common environmental effects (C) fitted to the BMI data better than the saturated or other sub-models. Consequently, subsequent longitudinal growth models for BMI were fitted on the bases of additive genetic and specific environmental influences (AE) parameterization.

The latent growth modeling resulted in a best-fitting model (Figure 4) including additive genetic and specific environmental influences for both BMI Level (A=60%, 95%CI: 45-71%; E=40%, 95%CI: 29-55%) and BMI Slope (A=64%, 95%CI: 45-75%; E=36% 95%CI: 24-55%). Level and Slope showed significant genetic and environmental correlations (r_g=0.40 95%CI: 0.15-0.65; r_e= -0.24, 95%CI: -0.44- -0.04). The overall genetic influences on BMI (or heritability estimates) had a consistent increasing trend, from 54% (95%CI: 42-65%) at wave 1 to 72% (95%CI: 61-79%) at wave 5.



Note: Numbers represent standardized estimates (and 95% Confidence Intervals) of percentage of variances accounted for by additive genetic (A) and specific environmental (E) influences on BMI Level, BMI Slope and mobility Level. Estimates on curved arrows represent genetic and environmental correlations between BMI Level, BMI Slope and mobility Level. Es_x stands for specific environmental influences with no effects across time. h^2 represent standardized estimates of the overall genetic influence (or heritability) on BMI or mobility in every occasion.

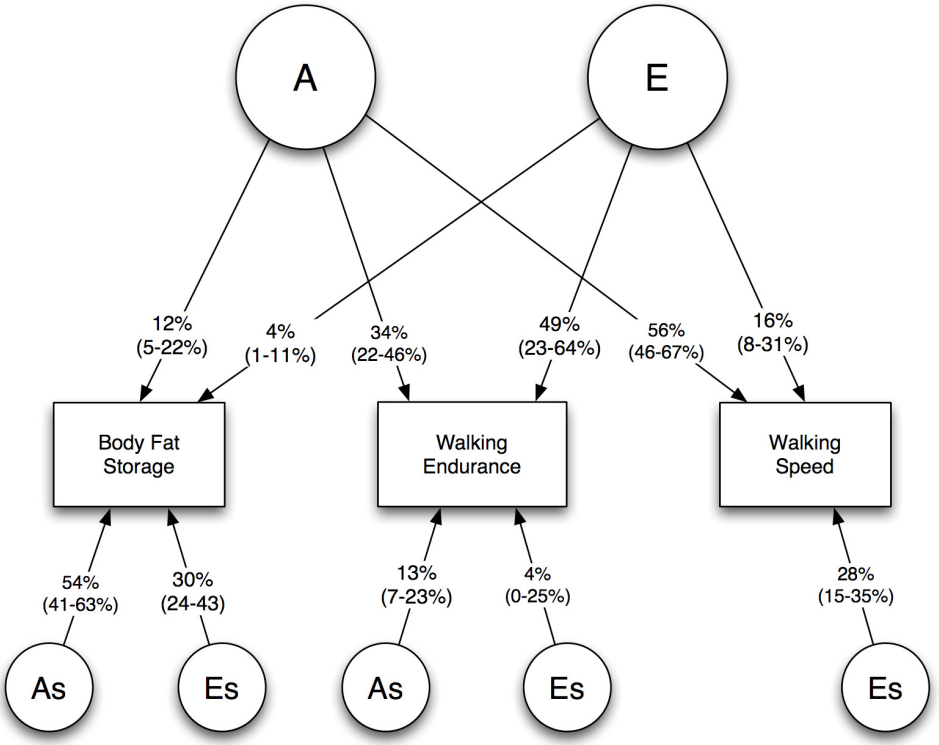
FIGURE 4 Summary model of lineal growth models for BMI over a 29-y period

By studying the variance-covariance matrices processed in the genetic modeling, we were able to observe the longitudinal evolution of the genetic and environmental variances detected at the beginning of the study. The results indicated that baseline genetic influences had an important though slightly decreasing residual effect in subsequent waves, explaining 82% of the variance at wave 5. The analyses also confirmed a minor proportion of new genetic influences (1 to 2%) emerging at every wave. These new genetic influences had

an expanding residual effect across subsequent follow-ups so that at the end of the study around 18% of the genetic variance was due to genetic influences that were not present at the baseline. Similarly, it was also observed that baseline environmental influences had a major but decreasing residual effect across subsequent follow-ups, while a minor proportion of new environmental influences emerged at every follow-up, with expanding residual effects in later waves. At the end of the study about 42.4% of the environmental variance was due to environmental influences not present at the baseline. The results also indicated that 4 to 13% of the total variance at every wave was explained by environmental factors (and measurement error) exclusive to each occasion (that is, with no effects earlier or later in time).

5.5 Study 4: The genetics of the cross-sectional relation between body fat and mobility in older women

The results of fitting the independent pathway model suggested a common genetic background between the body fat percentage, walking speed and endurance. In that final model, a negative phenotypic correlation between body fat and walking speed (r_{P1}=-0.32, 95%CI: -0.42 – -0.23) was observed, which was largely due (80%, 95%CI: 55 – 96%) to cross-trait genetic effects. An analogous negative phenotypic correlation between body fat and walking endurance (r_{P2}=-0.33, 95%CI: -0.42 – -0.24) was detected, that was largely due (66%, 95%CI: 35 – 79%) to the effect of shared genes. Cross-trait genetic influences accounted for 12% (95%CI: 5 to 22%) of body fat, 56% (95%CI: 46 to 67%) of walking speed and 34% (95%CI: 22 to 46%) of walking endurance. Additional trait-specific genetic influences were detected for body fat (54%, 95%CI: 41 to 63%) and walking endurance (13%, 95%CI: 7 to 23%). These results are summarized in Figure 5.



Notes: A and E refer to additive genetic and specific environmental influences respectively that are common to the phenotypes under study. As and Es refer to additive genetic and specific environmental influences respectively that are specific to each of the phenotypes. Numbers in arrows (and in brackets) are standardized estimates (and 95% confidence intervals) showing the proportion of additive genetic and specific environmental components of variance for every phenotype.

FIGURE 5 Summary model explaining the relation between the body fat content, walking speed and endurance phenotypes

A minor proportion of the phenotypic correlations of walking speed and endurance with body fat (r_{P1} and r_{P2}) were due to the shared effect of environmental factors. This cross-trait effect of environmental factors accounted for 4% (95%CI: 1 to 11%) of the influences on body fat, 16% (95%CI: 8 to 31%) of those on walking speed and 49% (95%CI: 23 to 64%) of those on walking endurance. Additional trait-specific environmental influences were also present for body fat (30%, 95%CI: 24 to 43%), walking speed (28%, 95%CI: 22 to 35%) and endurance (4%, 95%CI: 0-25%).

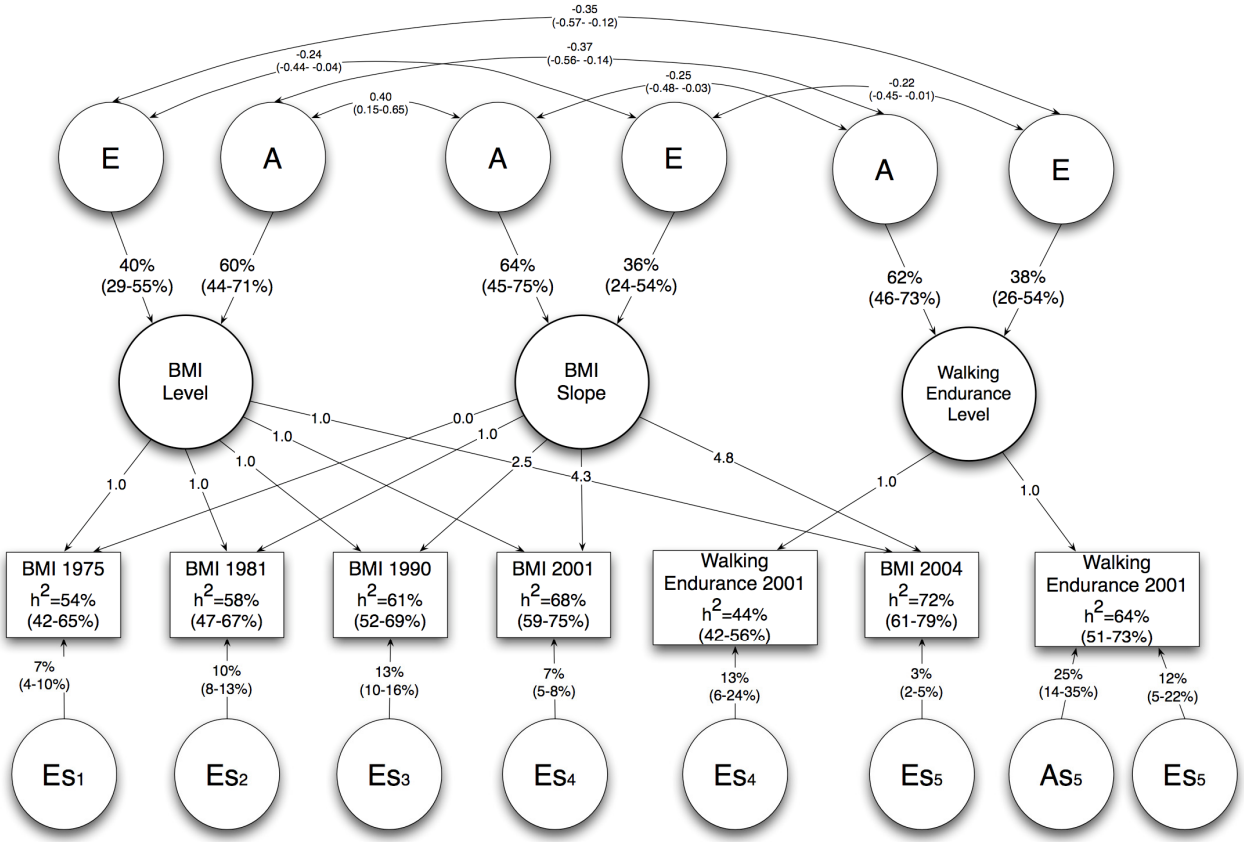
In addition, the two walking phenotypes were also highly correlated (r_{P3}=0.72, 95%CI: 0.63 – 0.75); this was mostly due (62%, 95%CI: 46 – 71%) to the effect of common genetic influences.

5.6 Study 5: the genetics of the longitudinal relation between adult body mass index and mobility level later in life

Table 4 shows means (95%CI) and ICCs for BMI and walking endurance. Age-adjusted linear regression analyses for complex samples showed that BMI and BMI rate-of-change across waves predicted walking endurance later in life ($p<0.001$; $R^2=0.10$-0.14).

Because the preliminary Cholesky decompositions for BMI and walking endurance confirmed that an AE sub-model fitted the data better than the ACE model or other sub-models, subsequent longitudinal growth models including BMI and mobility variables were fitted on the bases of an AE parameterization. The resulting best-fitting growth model (Figure 6) included additive genetic and specific environmental influences (AE) for adult BMI *Level* (A=60%), BMI *Slope* (A=64%), and Mobility *Level* at older age (A=63%). There were shared genetic and environmental influences between BMI *Level* and *Slope* (genetic correlation: r_g= -0.24; environmental correlation: r_e=0.40), between BMI *Level* and Mobility *Level* (r_g=-0.37, r_e=-0.35), and between BMI *Slope* and Mobility *Level* (r_g=-0.22, r_e=-0.35).

The heritability of BMI (or overall genetic influence on the trait) showed a consistent increasing trend, from 54% at wave 1 to 72% at wave 5. Similarly, the overall heritability of mobility increased from 44% at wave 4 to 64% at wave 5. Finally, results also indicated the presence of environmental factors exclusive to each occasion, which explained 4 to 13% of the total variance at every wave.



Note: Numbers represent standardized estimates (and 95% Confidence Intervals) of the percentage of variances accounted for by additive genetic (A) and specific environmental (E) influences on BMI Level, BMI Slope and mobility Level. Estimates on curved arrows represent genetic and environmental correlations between BMI Level, BMI Slope and mobility Level. Esx stands for specific environmental influences with no effects across time. h2 represent standardized estimates of the overall genetic influence (or heritability) on BMI or mobility in every occasion.

FIGURE 6 Summary model (lineal growth) for genetic and environmental influences on BMI over 29 year and its impact on Mobility level later in life

6 DISCUSSION

6.1 Genetic and environmental influences on late life mobility performances

The results of this investigation study showed that, among community-living older women in relatively good health, common additive genetic influences accounted for both maximal walking speed and endurance. Previous studies using genetic models have also reported moderate amounts of additive genetic influences on maximal walking speed for older women (Leinonen et al., 2005, Pajala et al., 2005). Customary walking speed among older male twins was found to receive a similar influence from genes (42%)(Carmelli et al., 2000a) compared to those found among female twins. There are, therefore, relatively minor differences between men and women in the genetic influences, despite the disparities of the walking test used (customary instead of maximal walking speed), as well as of the gender of the study sample (as there are gender differences in the physiological requisites underlying walking ability e.g., leg strength). Nevertheless, as far as we are aware, there are no previous studies on the heritability of walking endurance or on the shared genetic and environmental influences between maximal walking speed and walking endurance phenotypes.

The immediate physiological requirements for walking any distance are sufficient lower extremity strength and postural balance, and, with increasing distance, also oxygen uptake capacity. As these physiological prerequisites for walking have proven to be moderately to highly influenced by genes (Bouchard et al., 1998, Katzmarzyk et al., 2001, Pajala et al., 2004), it is likely that part of the moderate genetic influences present in walking speed and endurance are genetically related to influences underlying its physiological requisites. For example, as obesity increases the risk of walking limitation (Thomis et al., 1997, Lamb et al., 2000) and as it is also highly genetically influenced (Nelson et al., 1999), the genetic mechanism on walking speed and endurance may be also

mediated through genes underlying a predisposition to gain weight (Pajala et al., 2005, Tiainen et al., 2007).

In the longitudinal analyses, genetic influences on walking speed remained stable and at a moderate level over a 3-year follow-up, while genetic influences on walking endurance increased somewhat. The genetic influences at baseline and follow-up were highly correlated, suggesting expression of the same genes at both time points. The results also suggested a minor proportion of newly expressed genetic influences at follow-up for both phenotypes.

Knowledge about the evolution of genetic influences and changes in the heritability of mobility performances across time has to date been very limited. A previous experimental animal study found that in several groups of selectively inbred mice changes in the genetic influences on mobility occurred across time, suggesting an interaction between genetic background and age on mobility (Turner et al., 2005). The results in the present study suggested also a small increase in the total phenotypic and genetic variability over the study period for both walking tests. Christensen et al described analogous changes in genetic variances for self-reported physical functioning in older women in a 6-year follow-up study (Christensen et al., 2003). It seems, then, that increased genetic variability in physical functioning at older ages reflects increasing genetic variance in the underlying physiological prerequisites. A possible explanation for this phenomenon offered by Christensen is based on genetic-evolutionary theories of aging, which suggest that genetic variability in the underlying phenotypes for physical functioning tend to vary more at older ages due to changes in gene expression in different body systems or the weakening influence of beneficial genes that were strongly active earlier in life. Further support to this hypothesis is given by recent studies showing that more than 100 genes involved in body metabolism were under-expressed in older women compared to younger (Welle et al., 2004).

Our results show also that the variability due to environmental influences increased for walking speed, while it conversely decreased for walking endurance. This would initially suggest that for walking endurance the genetic influences would tend to have more impact with age, while the importance of environmental influences would decrease. This observation seems somewhat supported by an overall sample decline in habitual walking (km/week) with age. Environmental factors such as habitual physical activity or diet are well known to influence short and midterm evolution of older women's mobility. For example, older women involved in exercise programs or simply following active lifestyles are less prone to develop mobility limitations than those with sedentary habits (Visser et al., 2002c). Habitual physical activity can successfully improve muscle endurance, strength, gait, and function. On the other hand, older women showing low serum carotenoid levels resulting from low intake of fruits and vegetables may have faster progression towards severe walking disability than those keeping a healthy diet (Semba et al., 2007). Persons with increasing body mass index in adulthood, resulting from poor eating habits and low physical activity, tend to show poor walking

performances and an early onset of mobility limitations in late life (Stenholm et al., 2007b).

6.2 The genetics of obesity across adulthood

In the present study, genetic influences on BMI increased consistently across the 5 waves of observations, from 54 to 72%. This increment was partly due to the persistence and expansion of baseline genetic effects during the study period. However, new genetic influences also emerged at every wave, accounting for 18% of the BMI heritability at wave 5. Previous twin studies on adult women have suggested that genetic effects on BMI tended to remain stable across time (Korkeila et al., 1995, Austin et al., 1997). However, these studies were shorter, had a single follow-up, or the twins were in a different age-range compared to those in the present study.

These results from the present investigation suggested that some gene expressions relevant to weight regulation over time may switch off and on while aging. A comparable result was reported by Fabsitz et al. in a 43-year follow-up twin study of adult men, with one stable component across time, and a different subset of genetic influences arising mostly in late adulthood (Fabsitz et al., 1992). It seems that in both men and women the genetic etiology of BMI may vary across the lifespan (Hewitt, 1997), with some obesity-related genes expressing only at a given time in life (Fabsitz et al., 1992).

Our results suggest that there may be a subset of genes predominantly influencing the rate of change in BMI, and another subset that has more stable effects on BMI across adult life, and that these two subsets had a positive genetic correlation of 0.40. This genetic correlation may be considered as a measurement of pleiotropy, indicating that a share of the genes influencing higher BMI on a given occasion were moderately responsible for the positive growth in BMI over time. This finding of two subsets of genes with possible shared effects is in line with earlier investigations among different twin samples (Austin et al., 1997). For example, in recent analyses of 15 years of data on BMI from the entire Finnish twin cohort, the result showed some proportions of shared and specific genetic influences in BMI level and rate-of-change (Hjelmborg et al., 2008). This is supported by further observations at the molecular level. For instance, while the Pro1019Pro Lepr polymorphism in particular is associated with both high adiposity and longitudinal gains in BMI, (de Silva et al., 2001) there are some studies proposing additional genes (e.g. APO-E gene, the uncoupling protein 1 gene and the B3-adrenergic receptor gene polymorphisms) as specific regulators of longitudinal increments in adult body weight (Gueguen et al., 1989, Clement et al., 1995, Sivenius et al., 2000). Yet, these specific genes have not been widely replicated as predictors of long-term weight gain.

These results suggest that searching for genetic variants specifically accounting for the rate of change in BMI across the lifespan may be worthwhile (Comuzzie et al., 1998, Rankinen et al., 2006b). Several investigations conducted within the Framingham Heart Study have shown evidences for genetic linkage explicitly for long-term increasing BMI in chromosome 4 (Strug et al., 2003) and for long-term weight change in chromosome 1 and 20 (Fox et al., 2005). Nonetheless, gene-gene interactions are very likely to make an important contribution to obesity-related phenotypes (Warden et al., 2004, Yi et al., 2004). Evidences suggest that these sets of genes are likely to work in interaction not only with each other but also with short and long-term environmental influences and body stressors, such as physical activity and diet (Samaras et al., 1999, Attie et al., 2003, Pilegaard et al., 2003). Thus, the efficiency of this long-term genetic mechanism leading to overweight and obesity would rely to a certain extent upon its interaction with environmental influences, thereby determining the final phenotypic expression.

Our analyses identified a minor increasing trend with age in the environmental variance of BMI. The results showed that baseline environmental factors had residual effects accounting for 59% of the environmental variance at the end of the study. This implies several important phenomena not reported earlier: firstly, the presence of short-term environmental factors with moderately persistent effects across occasions; secondly, the appearance at different times of small proportions of new environmental factors with cumulative and expanding residual effects later in life; and, thirdly, the occurrence of short-term environmental influences with no effects earlier or later in life. Our results also indicated a negative environmental correlation between the stable component of BMI and the change in BMI across time. This negative correlation suggests the possibility of certain persistent environmental influences during the course of the study that may be responsible for a negative growth in BMI, in contrast with the positive growth due to genetic sources.

The study from Fabsitz and colleagues indicated that although environmental factors in men were consistently present, they changed substantially from one occasion to another, indicating great volatility (Fabsitz et al., 1992). The present study showed not only a proportion of environmental influences of limited duration, but also environmental influences persistent over time. This observation may concur with socio-epidemiological findings. For example, for some persons aspects related to socioeconomic status (e.g. education, marital status, work environment, job demands or hours worked), tend to remain stable in mid-life and may have prolonged effects on body composition (Rissanen et al., 1991, Lahti-Koski et al., 2000, Molarius et al., 2000, Brown et al., 2003) while there may be changes to them with age (e.g. retirement, widowhood, etc) thereby contributing to fluctuations in BMI. Nevertheless, the cause-effect relationships between socio-economic variables and body weight remain poorly understood (Sarlio-Lahteenkorva, 2007).

Our final growth model showed opposite signs in the genetic and environmental correlations, indicating that long-lasting genetic and

environmental influences on the rate of change in BMI may, to some extent, operate in different ways. It is possible that women genetically prone to high BMI may keep their BMI within certain bounds through modification of environmental factors that may ameliorate growth of BMI in adulthood (Fabsitz et al., 1994, Samaras et al., 1999, Waller et al., 2008). It seems, then, that women who were initially leaner due to environmental reasons are likely to sustain their leanness until older ages, but on the other hand they are likely to gain weight due to, for instance, unsustained or fluctuating healthy behaviors. Observational and interventional studies as well as clinical experience have demonstrated that it is difficult to maintain behaviorally mediated weight loss in the long-term, for example through dieting or increased amounts of daily physical activity (Kramer et al., 1989, Sarlio-Lahteenkorva et al., 2000, Schmitz et al., 2000).

6.3 Genetic and environmental influences explaining the relation between obesity and mobility

6.3.1 The cross-sectional relation between obesity and mobility

Several large epidemiological trials have evidenced a link between higher BMI, poor mobility and frailty. For example, analyses done at the Women Health and Aging Study (WHAS) I and II showed that obesity was associated with FS in older women (Blaum et al., 2005). Clinical characteristics of the FS (poor walking ability, muscle weakness, poor exercise tolerance, late life unintentional weight loss and exhaustion) tend to be more common among older persons with overweight and obesity than those with normal body weight, suggesting that the mechanisms leading to disability and frailty may be more common in older persons with high BMI, but without depending entirely on BMI.

The results presented in this dissertation suggested that the observed association between adiposity and mobility in older women was due mostly to the effect of shared segregating genes. These genes represented a minor proportion of the overall body fat genotype, although they corresponded to major parts of the walking genotypes. Moreover, genes predisposing to higher adiposity underlay poorer walking performances, and vice versa.

Knowledge about the biological pathways governing the relation between obesity and mobility in humans is limited. Animal models have shown that genetic selection for low mobility was underlain by metabolic changes that led to high blood pressure, hyperinsulemia, increased blood triglyceride concentration and high adiposity (Wisloff et al., 2005). Rats with low mobility had low amounts of key proteins for mitochondrial function in muscle, implying that a genetically induced impaired metabolism could be responsible

for the link between reduced mobility performance, high adiposity and development of metabolic and cardiovascular disorders in older individuals.

Recent analyses have shown that in older persons, genes controlling metabolism (glucose metabolism, fatty acid metabolism, TCA cycle, mitochondrial electron transport, ATP production, mitochondrial ribosomal proteins, creatine synthesis and transport and import of proteins into mitochondria) seem under-expressed among older compare to younger women (Welle et al., 2003) with more than 100 already identified (Welle et al., 2004). Further studies have also targeted the role of specific genes that seem to be key mediators in metabolism. For instance, a reduced expression of the peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) gene (a transcriptional co-activator essential for mitochondrial biogenesis mediating muscle fiber type switching) (Attie et al., 2003, Puigserver et al., 2003) may provoke inefficient glucose oxidation, insulin resistance, poor muscle function and increased body fat storage (Attie et al., 2003).

This reduction of proteins in muscle cell may be also connected with sarcopenia and inflammation. Sarcopenia is the involuntary loss of skeletal muscle that occurs with advancing age. Cross-sectional and longitudinal data have shown that sarcopenia is commonly associated with decreased muscle mass, strength and endurance and increased fat mass (Visser et al., 2005, Fantin et al., 2007). Therefore sarcopenia and obesity are usually concomitantly present, and may explain part of the association between obesity and mobility (Roubenoff, 2000). The events leading to sarcopenia are still unclear and likely multifactorial, encompassing genetic and environmental factors and their interactions (Roubenoff, 2000). Sarcopenia is normally characterized by a decrease in protein synthesis and an increase of inflammatory markers, suggesting that several inflammatory processes may underlie the relation between increased fat mass and decreased muscle mass. For example, there is a gradually impaired regulation of cytokine protein expression with age that may have catabolic effects on muscle and anabolic effects on fat mass. Thus, inflammatory markers such as IL-6 or TNF-α, produced by adipocytes, are consistently related to progressive insulin resistance, high fat mass and a loss of muscle mass, strength and mobility (Argiles et al., 1997, Paolisso et al., 1998, Visser et al., 2002b). Inflammatory markers have shown to be genetically influenced to an important extent. For example, the heritability of IL-6 ranged between 17-61%, while the corresponding values for C-reactive protein and TNF-α were 20-56% and 26%, respectively (de Maat et al., 2004, Wessel et al., 2007, Su et al., 2008). This inflammatory process that enhances catabolic mechanisms also promotes the onset of insulin resistance, reducing the dietary energy intake and lowering the concentrations of other key proteins, such as insulin-like growth factor 1. In this context, obesity-related medical conditions, which are considered major mediating factors in the relation between obesity and mobility, tend to appear (e.g. type-2 diabetes or hypertension). It has been suggested that the genes influencing inflammatory markers such as CRP may exert pleiotropic effects (shared genetic determination) for BMI, and other

obesity related phenotypes, such as leptin serum concentration or triglycerides (Wessel et al., 2007). These suggestions are supported at a molecular level, and a decreased frequency in males of the -174C polymorphism in the promoter region of the IL-6, for example, is associated with higher levels of IL-6, increased BMI and insulin resistance (Barbieri et al., 2005).

These genes may not work however in isolation but rather in interaction with crucial environmental influences and body stressors, such as physical activity and diet. Habitual physical activity for instance, induces an increase in PGC-1α transcription that may also coordinate the activation of other metabolic genes in human muscle (Pilegaard et al., 2003). Visser et al. showed that plasma concentrations of inflammatory markers e.g. IL-6 and TNF-α in well-functioning older individuals were inversely associated with muscle mass and strength. Roubenoff et al. hypothesized also that these inflammatory processes might represent a vicious cycle between fat gain and muscle loss with environmental factors such as physical activity as a link that would limit mobility synergistically (Roubenoff, 2000). That is, increased fat mass results in loss of muscle cells, reduced resting metabolic rates and decreased physical activity level. With physical activity becoming increasingly difficult, the habitual level of physical activity decreases further as a result of continuously and gradually growing fat mass. Other studies have shown that resistance exercise and CR induces a decrease in inflammatory markers, such as muscle TNF-α expression (Greiwe et al., 2001, Phillips et al., 2005).

Besides, the effects of physical activity and diet together may also interact with genetic influences. For example, reduced calorie intake increases protein metabolism and improves the genetic mechanisms mediating insulin sensitivity in aging muscle (Lee et al., 1999), while increased dietary intake may increase lipogenesis primarily by boosting the genetic transcription of hepatic lipogenic enzymes, such as fatty acid synthase (FAS) (Goodridge et al., 1986, Goodridge, 1987). At the same time, habitual physical activity also down-regulates genetic transcription of FAS and so attenuates dietary induction of hepatic FAS and reduces lipogenesis (Fiebig et al., 1999). Thus, efficiency in the genetic mechanism linking mobility and adiposity in older individuals seems to rely to a high extent upon their interaction with environmental influences.

6.3.2 The longitudinal relation between obesity and mobility

In the present study, the genetic effects on BMI (*Level* and *Slope*) had a negative correlation with mobility *Level* later in life (-0.37 and -0.25, respectively). This indicates that genes predisposing to higher BMI across middle age moderately account for poorer mobility in older age. Although the biological mechanisms are uncertain, there are some data that may suggest longitudinal pathways. Given that skeletal muscle is the primary site for glucose and triglyceride utilization (Lithell et al., 1981, Dinneen et al., 1992), age-related muscle loss may contribute to peripheral insulin resistance, dyslipidemia and increased adiposity (Greiwe et al., 2001). It has been suggested that a progressive

impairment of the genetic regulation of cytokine protein expression with age may play a central role in the longitudinal relation. For example, the genetic over-expression of TNF-α in muscle cells suppresses the expression of the lipoprotein lipase enzyme, gradually increases body fat storage, and simultaneously induces muscle loss and cell death (Greiwe et al., 2001).

However, these genes are likely to work in interaction not only with each other (Warden et al., 2004) but also with short and long-term environmental influences and body stressors, such as physical activity and diet. For instance, resistance training and calorie restriction decrease muscle TNF-α expression (Greiwe et al., 2001, Phillips et al., 2005), which may also coordinate the activation of other metabolic processes. Thus, this shared genetic mechanism underlying long-term changes in BMI and late life mobility would rely to a certain extent upon an interaction with environmental influences. Gene-exercise/diet interaction may regulate several metabolic processes and improve mobility by changing the expression of different genes (Teran-Garcia et al., 2005) and by modulating muscle cell sensitivity to key proteins (Tuomilehto et al., 2001, Ozcelik et al., 2004). As a result, although the genetic mechanisms involved in muscle cell metabolism might have a strong influence on the process of fat storage and physical functioning, environmental prompts could determine the final phenotypic expression. Long-term commitments to exercising or healthy eating may prevent full realization of an individual's genetic predisposition to obesity (Hewitt, 1997) and so delay the onset of mobility disability.

6.4 Methodological considerations

Among the advantages of this research work were the use of population-based data and the relatively long follow-up. Moreover, mobility in old age (**Studies 1, 2**, **4** and **5**) was assessed using standardized measures of physical performance.

We nevertheless acknowledge that we used self-report data on weight and height in the first three waves of this longitudinal design (**Studies 3** and **5**). Previous studies using self-reported weight and height have noticed a so-called "flat curve effect", with heavier persons tending to report values somewhat regressed toward the population average (Kuskowska-Wolk et al., 1989). Therefore, the likelihood of reporting bias needs to be considered. However, the self-reported data on weight and height used here showed good reliability and accuracy when compared to the measured data (Korkeila et al., 1998, Silventoinen et al., 2000). In addition, the statistical models included estimates for specific environmental influences at each wave, which also captures potential measurement errors. Thus the estimates for the genetic influences on BMI are in turn adjusted for the potential effects caused by the difference between the first three and the last two waves in the method of assessing BMI.

Thus the estimates for the genetic influences on BMI are in turn adjusted for the potential effects caused by differences in assessment methods of BMI between the first three and the last two waves. Genetic and environmental variances increased consistently across waves, regardless of the way of measuring the phenotype. This makes it unlikely that the observed increment in the heritability during the follow-up period could be entirely explained by differences in the accuracy of self-report versus measured weight and height.

In **Studies 3** and **5**, the analyses focused on estimating the influences underlying a linear rate-of-change in BMI. Therefore populations or age groups, such as children, where BMI may well follow other trends (e.g. quadratic, exponential or logarithmic) are likely to show a different result. In our data, the observed increment in BMI was mostly due to weight gains in the study sample. However, a mean decrease of 3.6 cm in height over 29 years was also detected. Our study was limited to women without severe disability or extreme obesity, and therefore the results may not be directly generalizable to men and to people with poorer health. Finally, the moderate sample size with some fluctuations in size across the data collection waves may potentially restrict the statistical power in the genetic analyses by underestimating genetic dominance (D) or common environmental (C) effects. However, considering the good fit of the models and the narrow confidence intervals of the estimates, the data does not appear to be power-limited. Replication studies including higher number of twin pairs may be of help to confirm the results presented here.

6.5 Implications and future directions

The results presented here imply that identification of the specific genes involved in metabolism and the development of obesity in adults and older could lead to well-targeted interventions for preventing obesity, disability and frailty in older age. The possible detection of the specific genes with simultaneous effects on obesity and mobility may help to recognize those that require explicit exercise counseling programs aimed to decrease body weight and prevent mobility loss. As the study identified a subset of genes specifically accounting for long-term weight gain, it would be also worthy to investigate those genetic variants that specifically account for variability in rate-of-change across adulthood.

Future studies may deepen into the genetic relation between obesity and mobility by investigating the role of mediating phenotypes, such as muscle characteristics and sarcopenia. Poor muscle characteristics and sarcopenia are often present in older persons in combination with obesity and decreased mobility, and it is often referred to as *sarcopenic obesity syndrome*, with possibly common pathogenic influences for sarcopenia, increased body fat and reduced mobility (Villareal et al., 2004). These potential etiopathogenic links between obesity, sarcopenia and mobility disability remain poorly understood and

further analyses should focus on investigating possible common genetic variants influencing subcutaneous, intramuscular or visceral fat, muscle characteristics and mobility performances in older persons.

In addition, coming studies should also provide further understanding of why some people remain overweight or obese at very old ages while other lose weight and decrease BMI. In this way, it may be possible that genetic influences may underlie as well the decrease in body weight and BMI usually seen in older persons at earlier stages of the geriatric syndrome of frailty.

The mechanisms behind the gene-exercise/diet/drug interaction are currently under investigation with the aim of definitively understanding how changes in lifestyle toward increasing physical activity, moderating diet or the use of certain medication may interact with genetic influences in preventing or treating obesity, metabolic diseases and mobility disability. Further studies should also be aimed at investigating in more detail the specific interaction of possible common genes for obesity and mobility with pharmacological and behavioral interventions. Nevertheless, while the genetic liability on the mechanism is been investigated, individual screening and modification of non-genetic factors remains the best approach to preserve or enhance walking ability. For this reason it is recommended that older women engage in healthy habits particularly regarding diet and physical activity. Finding ways to promote physical activity and good nutrition among older people may be the most feasible approach to preventing mobility loss.

7 MAIN FINDINGS AND CONCLUSIONS

The main findings of the present study can be summarized as follows:

1. Mobility in older age was moderately-to-highly influenced by genetic influences; while the genetic influences in walking speed seemed to remain stable in a 3-year follow-up, the genetics influences on walking endurance tend to increase. In both phenotypes, new genetic influences showed to emerge with increasing age.

2. The genetic influences on women's BMI showed a consistent longitudinal increment, from 54% at the age of 42 years, to 72% at the age of 71 years; this was partially due to new genetic influences that showed to emerge with age.

3. Genetic influences on BMI level across adulthood were partially responsible (r_g=0.40) for the increasing rate-of-change with age; genes affecting level of BMI (A_{level}=60%) may also differ from those affecting change in BMI with age (A_{slope}=63%).

4. A common genetic background explained 80% of the association between body adiposity and walking speed (r=-0.32), and 65% between body adiposity and walking endurance (r=-0.33); this common genetic background accounted for 12% of the variability in adiposity, 56% in walking speed and 31% in endurance.

5. Genes predisposing to longitudinal weight gain from middle to old age, and higher BMI moderately account (r_g=-0.25 / -0.37) for poorer mobility level later in life.

In conclusion, the results of the present study suggested that mobility and obesity were moderately to highly explained by genetic influences. The genetic predisposition to obesity tended to increase across adult life, with newly

expressed genetic influences increasing with age. Newly expressed genetic influences with age were also recognized in walking speed and endurance in a short follow-up. Importantly, there was a common genetic background between obesity and mobility phenotypes, and genes predisposing to higher BMI and weight gain from midlife onwards also account for poorer mobility in old age. The next step would be to identify specific genes and common genetic variants involved in human metabolism and mobility performances, which could lead to interventions targeted at preventing obesity and mobility loss later in life. However for the present, modification of environmental factors, such as exercise and nutrition, remain the most feasible ways of influencing BMI and mobility across the life span.

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