Adult life course determinants of cardiac structure and function in the Medical Research Council 1946 birth cohort

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Declarations of originality and copyright

I hereby declare that this work is original and authored by myself and all appropriate sources have been referenced.

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This thesis is the culmination of 3 years work. Over the course of this time, I have learnt a great deal about an area I knew little about prior to starting – life course cardiology and life course echocardiography in particular. I am glad that the challenge of research combining my two areas of special interest (heart failure and imaging) with cardiovascular epidemiology was one that I took up as it has led to a most fruitful, enjoyable and interesting time in my career.

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Finally, I would like to thank my mother for all she has done to help me in my achievements to date.

Dedication

This thesis is dedicated to my daughter Saranya.

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Overview of my roles and responsibilities

I joined the MRC NSHD in October 2009 as a PhD student to improve the echocardiographic data collection process, clean, analyse and interpret the data from a life course perspective. I submitted my thesis in December 2012.

Analytical responsibilities

- I developed the life course models and carried out the statistical analyses and interpreted the results with guidance from Professor Rebecca Hardy, an expert statistician in life course methodology and Professor Alun Hughes
- I presented the data nationally and internationally to my peers and members of the public at conferences, media events and the Houses of Parliament
- I have submitted derived papers to journals for consideration of publication
- I am lead author for submitted manuscripts detailing the echocardiographic outputs of this study and have submitted derived papers to journals for consideration of publication
- I am collaborating author on all work referencing the echocardiographic data

Study design and quality-control responsibilities

- I modified the data collection protocol and data analysis protocol under the guidance of Professor Alun Hughes
- I was responsible for maintaining quality-control standards for the echocardiography data collection, providing regular feedback to the technicians in the clinical research facilities and organizing refresher training
- I carried out phantom calibration of the echocardiogram machines at all clinical research facilities
- On the rare occasion that echocardiographers were not available I scanned participants (<10 occasions).
- I analysed one third of the echocardiograms (512)
- I designed the reproducibility exercise for the readers
- I took part in the reproducibility exercise and analysed the results
- I took part in data coding
- I cleaned the echocardiography data and blood pressure data under the supervision of Professor Rebecca Hardy

Prizes, presentations and publications related to my research

Awards, prizes and recognition

2013	March	**Winner - Travel grant to present research overseas**	British Cardiovascular Society
	March	**Abstract chosen for media publicity (BMI-LVMI abstract)**	American College of Cardiology
2012	September	**Winner - Young Investigator of the Year Award**	British Society of Hypertension
	June	**Finalist, Cardiology Section President's Medal**	Royal Society of Medicine
	May	**Travel grant award in recognition of high-scoring abstract**	British Cardiovascular Society
	March	**Top ranked abstract from the UK (DM-LVMI abstract)**	American College of Cardiology
	March	**Abstract chosen for media publicity (HTN-LVMI abstract)**	American College of Cardiology
2011	September	**Finalist - Young Investigator of the Year Award**	British Society of Hypertension

Publications

Papers

2012

March	**Population heterogenecity in trajectories of midlife blood pressure**	Willls AK, Lawlor DA, Muniz-Terrera G,

	Epidemiology 2012;23(2):1-9	Matthews F, Cooper R, *Ghosh AK* et al.

2011

February	**Cohort Profile: Updating the cohort profile for the MRC National Survey of Health and Development: a new clinic-based data collection for ageing research** *International Journal of Epidemiology* 2011;40(1):e1-9	Kuh D, Pierce M, Adams J, Deanfield J, Ekelund U, Friberg P, *Ghosh AK*, et al.

Abstracts

2013

August	**Age at first detection of overweight and adult life course BMI are associated with future diastolic dysfunction** *Eur Heart J 2013 (in press)*	*Ghosh AK*, Hughes AD, Francis D, Chaturvedi N, Kuh D, Deanfield J, Pellerin D, Mayet J, Hardy R
	Age at first detection of overweight and adult life course BMI are associated with future increased left ventricular mass index *Eur Heart J 2013 (in press)*	*Ghosh AK*, Hardy R, Francis D, Chaturvedi N, Kuh D, Deanfield J, Pellerin D, Mayet J, Hughes AD
March	**Adult life course body mass index and age at first detection of overweight are associated with future increases in left ventricular mass index** JACC 2013; 61 (10_S):E1344	*Ghosh AK*, Hughes AD, Francis D, Chaturvedi N, Kuh D, Deanfield J, Pellerin D, Mayet J, Hardy R

2012

September	**Is it time for a new look at the "watch and wait" approach – mid-life antihypertensive treatment may not normalize left ventricular mass in spite of controlled blood pressure** *Journal of Human Hypertension* 2012;26:S1	*Ghosh AK,* Hardy RJ, Francis DP, Chaturvedi N, Pellerin D, Deanfield J, Kuh D, Mayet J, Hughes AD
August	**High systolic blood pressure and increased rate of rise of blood pressure in mid-life predict impaired diastolic function in the elderly (The MRC NSHD)** *Eur Heart J 2012;33(Suppl 1):361*	*Ghosh AK,* Hardy RJ, Francis DP, Chaturvedi N, Pellerin D, Deanfield J, Kuh D, Mayet J, Hughes AD

April	**Time for a review of the "watch and wait" strategy for young borderline-hypertensives?** *Heart* 2012;98:A77	*Ghosh AK*, Hardy RJ, Francis DP, Chaturvedi N, Pellerin D, Kuh D, Deanfield J, Mayet J, Hughes AD
	Increase in left ventricular mass in type 2 diabetes is dependent on duration of diabetes *Heart* 2012;98:A77	*Ghosh AK*, Hughes AD, Francis DP, Chaturvedi N, Pellerin D, Kuh D, Deanfield J, Mayet J, Hardy RJ
March	**Mid-life antihypertensive treatment may not normalize left ventricular mass in spite of controlled blood pressure** *JACC* 2012;59:1722	*Ghosh AK*, Hardy RJ, Francis DP, Chaturvedi N, Pellerin D, Kuh D, Deanfield J, Mayet J, Hughes AD
	Duration of diabetes is a significant independent predictor of elevated left ventricular mass *JACC* 2012;59:1727	*Ghosh AK*, Hughes AD, Francis DP, Chaturvedi N, Pellerin D, Kuh D, Deanfield J, Mayet J, Hardy RJ

2011

December	**Elevated systolic blood pressure from the age of 36 years onwards can predict left ventricular mass at ages 60-64 years independent of sex and treatment for hypertension (The MRC NSHD)** *European Journal of Echocardiography* 2011;12(Suppl 2):ii43	*Ghosh AK* et al**.**
October	**The effect of life course systolic blood pressure on interventricular wall thickness** *Journal of Human Hypertension* 2011;25:629	*Ghosh AK* et al**.**

Presentations

Oral

2013

February	**Lessons in preventive Cardiology from the UK MRC 1946 birth cohort**	Calcutta National Medical College Reunion Scientific Sessions, Calcutta

2012		
September	**Is it time for a new look at the "watch and wait" approach**	British Society of Hypertension Conference, Cambridge
August	**High systolic blood pressure and increased rate of rise of blood pressure in mid-life predict impaired diastolic function in the elderly (The MRC NSHD)**	European Society of Cardiology Conference, Munich
June	**Time for a new look at the "watch and wait" approach**	Royal Society of Medicine, London
2011		
September	**The effect of life course systolic blood pressure on interventricular wall thickness**	British Society of Hypertension Conference, Cambridge

<u>Poster</u>

2013		
August	**Age at first detection of overweight and adult life course BMI are associated with future diastolic dysfunction**	European Society of Cardiology Conference, Amsterdam
March	**Age at first detection of overweight and adult life course BMI are associated with future increased left ventricular mass index**	European Society of Cardiology Conference, Amsterdam

	Adult life course BMI and age at first detection of overweight are associated with future increases in Left Ventricular Mass Index	American College of Cardiology Conference, San Francisco
2012		
November	**The Effect of Mid-life Blood Pressure Change and Anti-Hypertensive Treatment on Subsequent Left Ventricular Mass - A Life Course Approach**	American Heart Association Conference, Los Angeles
May	**Increase in Left ventricular mass in type 2 diabetes is dependent on duration of diabetes**	British Cardiovascular Society Conference, Manchester
	Time for a review of the "watch and wait" strategy for young borderline-hypertensives?	British Cardiovascular Society Conference, Manchester
March	**Mid-life antihypertensive treatment may not normalize left ventricular mass in spite of controlled blood pressure**	American College of Cardiology Conference, Chicago
	Duration of diabetes is a significant independent predictor of elevated left ventricular mass	American College of Cardiology Conference, Chicago
2011		
November	**Elevated systolic blood pressure from the age of 36 years onwards can predict LVM at ages 60-64y independent of sex and treatment for hypertension**	European Society of Echocardiography Conference, Budapest

Planned Publications

Cardiovascular risk factors from early life predict future cardiac structural and functional abnormalities: a Systematic Review of the published literature - submitted

Effect of mid-life blood pressure change and treatment on subsequent left ventricular mass - submitted

High systolic blood pressure and increased rate of rise of blood pressure in mid-life predict impaired diastolic function in the elderly - submitted

Age at first detection of overweight and adult life course BMI are associated with future increased left ventricular mass index – at manuscript stage

Age at first detection of overweight and adult life course BMI are associated with future diastolic dysfunction – at manuscript stage

Duration of diabetes is a significant independent predictor of elevated left ventricular mass – at manuscript stage

Abstract

Background

Elevated blood pressure (BP) and body mass index (BMI) are associated with abnormalities of cardiac structure and dysfunction in cross-sectional studies. However the consequence of elevated BP and BMI over the adult life course on cardiac structure and function is unknown.

Methods

Participants in the Medical Research Council National Survey of Health and Development (MRC NSHD) 1946 birth cohort (n=1653) underwent investigations including echocardiography and BP and BMI measurement at age 60-64y. BP had been measured previously at ages 36, 43 and 53y and BMI had previously been measured at ages 20, 26, 36, 43 and 53y. The relationships between BP, treatment for hypertension (HTT) and BMI and echocardiographic determinants of cardiac structure and function at age 60-64y were investigated.

Results

Increased BP from age 36y onwards was associated with increased left ventricular mass index (LVMI) and poorer diastolic function (E/e'). This was independent of BP at age 60-64y for BP measured at age 53y. Faster rises of BP across mid-life were associated with greater increases in LVMI and E/e'. HTT was associated with increased LVMI and E/e' after adjustment for BP at age 60-64y. Associations with systolic function were inconsistent.

Increased BMI and overweight from the age of 20y onwards was associated with increased LVMI and poorer diastolic function. On including BMI/overweight at ages 60-64y, the associations remained for some ages (e.g. for ages 26y and 43y for LVMI and from age 36y onwards for E/e'). Earlier age at first detection of overweight was associated with increased LVMI and diastolic dysfunction. Associations with systolic function were inconsistent.

Conclusions

Increased adult life course BP and BMI are associated with increased LVMI and diastolic dysfunction. Increased rate of change in BP is associated with detrimental effects to cardiac structure and function as is HTT. Earlier age of first detection of overweight is associated with increased LVMI and diastolic dysfunction. Earlier interventions to prevent rapid rises in BP and the development of obesity may be key in preventing future abnormalities in cardiac structure and function.

Chapter 1

Introduction

Life course epidemiology

The life course approach

A life course approach to epidemiology investigates long-term biological, behavioural and psychosocial processes that link adult health and disease risk to physical and social exposures occurring in gestation, childhood, adolescence, earlier in adulthood or across generations.[1] The life course approach has been extensively used in epidemiology and has helped in the examination of biologic, genetic, social, and environmental determinants of health across the life course, leading to landmark insights into the relationship of early life (e.g. fetal development[2] or childhood socioeconomic position[3]) and later adult disease.

Recently some studies have employed a life course perspective to understand the early life determinants of cardiovascular disease. In particular, there has been a recent focus on applying life course methodology to blood pressure and its effects on future cardiovascular disease.[4-7]

History of the life course approach

Although the term "life course epidemiology" was coined in 1997, the idea that events occurring over the life course have effects in later life has been prevalent in the world of medicine for some time.[8]

In the 19th century the major focus was on infectious diseases which contributed significantly to mortality, especially mortality in children.[9] Towards the beginning of the 20th century there was a growing shift in emphasis onto early life influences on adult public health.[10] This trend affected public health policies on both sides of the Atlantic with the development of health services specifically targeted to the well-being of babies and children.[11]

A lot of work was carried out in the first half of the 20th century with the aim of studying growth and development; and pioneering work was carried out in the 1920's on what we would now recognise as the critical or sensitive period hypothesis. Work done on animals led to the formulation of a theory that there were critical periods in development during which exposures to deleterious agents had more of an influence than at other less-critical times.[12]

In the 1930s, a series of child health and nutrition studies were undertaken which looked at another mechanism of life course epidemiology – the accumulation hypothesis.[13, 14] This hypothesis postulates that the accumulation of deleterious environmental influences in childhood rather than exposures at critical periods could affect adult health.

Following World War 2, the accumulation hypotheses found more supporters. World War 2 army recruits were investigated to show that the accumulation of insults to health, starting in infancy, had an effect on adult health.[15]

However, post World War 2 there was also a shift in thinking away from trying to modify the early-life environment for better adult health. This was a consequence of a perception arising in the 1930s that in spite of improving child health, adult death rates had not fallen.[16] This shift in emphasis accelerated from the 1950s onwards with adult cohort studies which identified the risks to health associated with a multitude of factors which we would today class as classic cardiovascular risk factors (cigarette smoking, obesity, high blood pressure, high cholesterol and physical inactivity). Two such studies which have played major role in our understanding of adult cardiovascular risk were the Framingham cohort studies and Doll and Hill's study on UK doctors linking smoking to cardiovascular disease and lung cancer.[17, 18]

Another war led to a rekindling of interest in the possible childhood or early adulthood origins of cardiovascular diseases which were, at that time thought to be diseases of mid and late adult life. Autopsies of young soldiers killed in the Korean War demonstrated the presence of coronary atherosclerosis, till then thought to be a disease of middle-aged and elderly men.[19] Subsequent studies, notably the Pathobiological Determinants of Atherosclerosis in Youth study emphasized the early origins of fatty streaks and atherosclerosis[20] and the life course approach came to the forefront again in the 1990s with what is often termed the Barker hypothesis. Barker investigated the role of in-utero factors on adult heart disease leading to his seminal fetal origins of coronary disease paper in 1995.[2] This was followed by a number of studies linking both fetal (under-nutrition) and childhood (nutritional and socioeconomic status) characteristics with later adult cardiovascular disease.[21-24] The role of childhood

obesity with increased incidence of later metabolic syndrome and increased premature cardiovascular death was also explored at this time.[25]

Since the introduction of the term "life course epidemiology" in 1997,[8] there has been an expansion of the context in which the life course approach has been used both in terms of its application in age groups other than the fetal period and in terms of diseases other than cardiovascular disease. An illustrative example in respiratory disease is shown in Figure 1.1.

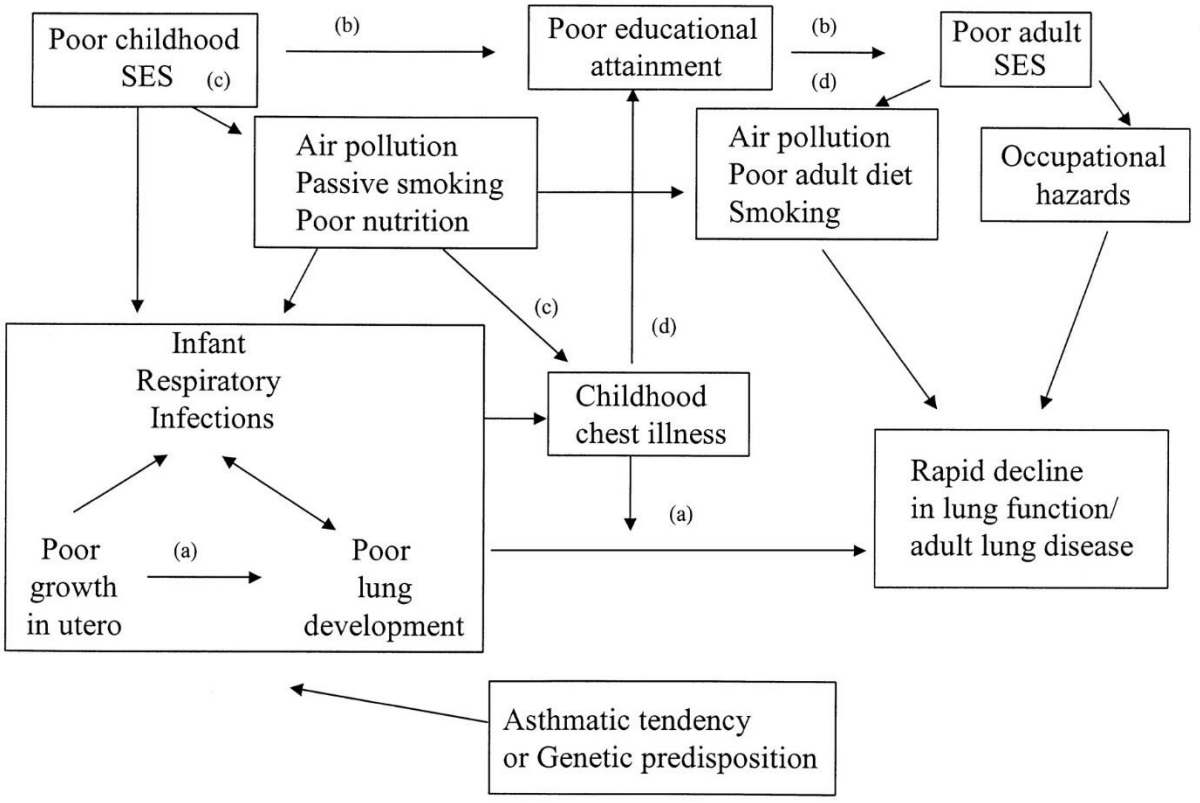


Figure 1.1. Life course model depicting life course effects on adult lung disease (after Kuh et al).[1]

There has been a general move towards placing chronic disease aetiologies within a life course framework with the World Health Organization recommending it in its non-communicable disease and health promotion programme.[27] The life course approach has expanded to use in the study of musculoskeletal function, health behaviours, reproductive health and the development of certain cancers.[28-30]

Very recently there has been a resurgence of interest in investigating the effect of risk factor changes over time (i.e. risk factor history) on subsequent cardiovascular disease with studies estimating the impact of changes in risk factors in mid-life on cardiovascular outcomes in late adulthood.[4-7] These studies have again brought to the fore the utility of the life course approach by providing evidence that elevated blood pressure at various stages in earlier life is associated with future cardiovascular morbidity and mortality in older age. However, what must be remembered when modelling risk factors across the life course, is that these risk factor trajectories can have their own life course predictors,[1] something that I will expand upon in the next few sections.

Life course and cardiovascular risk factors

Using a life course approach to understand the effects of cardiovascular risk factors would seem to be a logical thing to do. Identifying deleterious trends early may help prevent future morbidity and mortality and using a life course approach could lead to the discovery of sensitive time periods where intervention is likely to be most effective. A life course approach

to cardiovascular risk factors has been used in the literature which I will now discuss in more detail, focusing particularly on blood pressure and body mass index/being overweight.

Life course and blood pressure

The life course approach to adult blood pressure has most widely been applied to investigating the influence of fetal growth and childhood growth on later adult blood pressure. There have been fewer studies that have looked longitudinally at the effect of other risk factors on later adult blood pressure.

The fetal origins hypothesis introduced the concept that low birth weight was associated with higher blood pressure later in life. There was a proliferation of studies after that reaffirming the relationship (see Huxley et al[31] for a systematic review), although there were also dissenters.[24] Even when the effects of a variety of possible confounders e.g. social class,[32] alcohol intake,[33] maternal age[34] and maternal blood pressure[35] were taken into account, birth weight was shown in the majority of studies to have an independent relationship with adult blood pressure.

The exact mechanisms and causal pathway through which birth weight affects adult blood pressure have not been fully elucidated. Animal models have demonstrated that exposure to various environmental or nutritional factors during a sensitive period in early life can cause permanent defects at maturity (e.g. transient immunization of neonatal rats against growth hormone releasing factor results in permanent impairment of growth hormone secretion and thus growth rate)[36] and it has been postulated by Harding[37] that low birth weight may reflect

fetal under-nutrition which may cause permanent fundamental structural and physiological changes. These then become manifest in adulthood in the form of hypertension, insulin resistance, and increased predisposition to cardiovascular mortality. The role of maternal nutritional status may also need to be taken into account in relation to some adult chronic diseases, although it may not have a major role to play in adult blood pressure.[38, 39] It remains unclear whether poor maternal nutritional status acts by directly reducing fetal growth or through another mechanism.[40, 41]

The role of later growth in childhood on adult blood pressure has also been examined, to determine if there is a critical or sensitive period during growth in childhood that leads to elevated blood pressure in later adult life, with it being shown that weight at 1 year of age is not a predictor of adult blood pressure if current weight is known.[42] Some have argued that rather than poor fetal growth, a period of "catch-up growth" in infancy and early childhood is more detrimental and increases the risk of future type 2 diabetes mellitus and obesity.[41, 43, 44] Whether catch-up growth can predict adult blood pressure has also been tested with no association being demonstrated.[45] Poor childhood growth may be associated with raised adult blood pressure, although this may be due to related nutritional and socioeconomic issues.[46]

Although childhood and early adulthood weight has been shown to predict blood pressure in mid-life, earlier childhood weight does not seem to have an additional predictive value when current adult weight is known.[47] One of the difficulties in determining if childhood or early adult weight has a predictive value over and above later adult weight is the phenomenon of "tracking" which describes the relative stability of a certain characteristic over time.[48] This means that those individuals with a higher blood pressure than the population mean at a

younger age are likely to continue along that blood pressure trajectory such that at an older age they would have higher blood pressures compared to the population mean at that later age.[49-51] The same concept is applicable to BMI as well with obese children more likely to become obese adults.[52] Due to tracking, it is very difficult to determine in observational studies if earlier measures of a risk factor (e.g. blood pressure) independently influence future disease or whether their influence is mediated through being on a faster-rising risk factor trajectory compared to the population mean i.e. tracking.

The life course approach to blood pressure risk factors has been applied sparingly to older adults, but when it has (investigating the effect of BMI across life on blood pressure at age 45y), there has been a positive association.[53]

Life course and being overweight/obesity

Cardiovascular disease has been in decline since the 1960s in the USA and other parts of the developed world although there is some evidence that this decline is slowing if not reversing.[54] However, rising levels of obesity in both developed and developing countries has led to an "obesity epidemic"[55] with childhood obesity tripling over the last 30 years in the USA.[56] As a result, it has been suggested that there is likely to be a rise in deaths due to cardiovascular diseases.[57]

Applying a life course approach to obesity could be beneficial as it might allow targeted intervention at an appropriate stage. Alternatively, since once an individual becomes obese, it is very difficult to achieve permanent weight reduction, it could consequently be argued that measures to prevent obesity need to be implemented as early as possible.[58, 59] Identifying

a sensitive or critical period early on in childhood could help focus timings of interventions to check the increasing trend in obesity.

Many studies have investigated the association between birth weight and adult body mass index (BMI), showing a positive relationship.[60-63] The reasons are unclear, although proposed explanations range from increased fetal nutrition to hyperinsulinaemia.[64, 65] However studies looking at maternal under-nutrition and future adult body mass index have shown conflicting results with some studies showing an association between maternal under-nutrition and adult obesity,[66] while others have not shown such associations.[67]

The associations of weight in childhood and adolescence and later adult BMI are complex due to a number of possible confounding factors. Breast-feeding and catch-up growth appear to have a role. Breast-fed infants are less likely to be obese while those with rapid catch-up growth go on to develop increased BMI.[68, 69] The role of tracking has to be taken into account as described earlier.

Life course methodology

Life course methodology is complex and has evolved (and continues to evolve) with time.[70, 71] The influence of risk factors across the life course is generally viewed in terms of either "sensitive periods" or "accumulation of injuries". The sensitive period approach has also been

referred to as “biological programing” or a “latency model approach”.[72, 73] This approach has formed the basis of the fetal origins approach described earlier.[2] The accumulation hypothesis looks at the cumulative effect of a long-standing burden of exposure to a risk factor – longer exposure is likely to be worse although there may be a plateau in effect after a certain level of exposure has been reached.[26, 74, 75] The accumulation of exposure to risk factors can occur independently or they can be clustered (accumulation model with risk clustering) (Figure 1.2).[26]

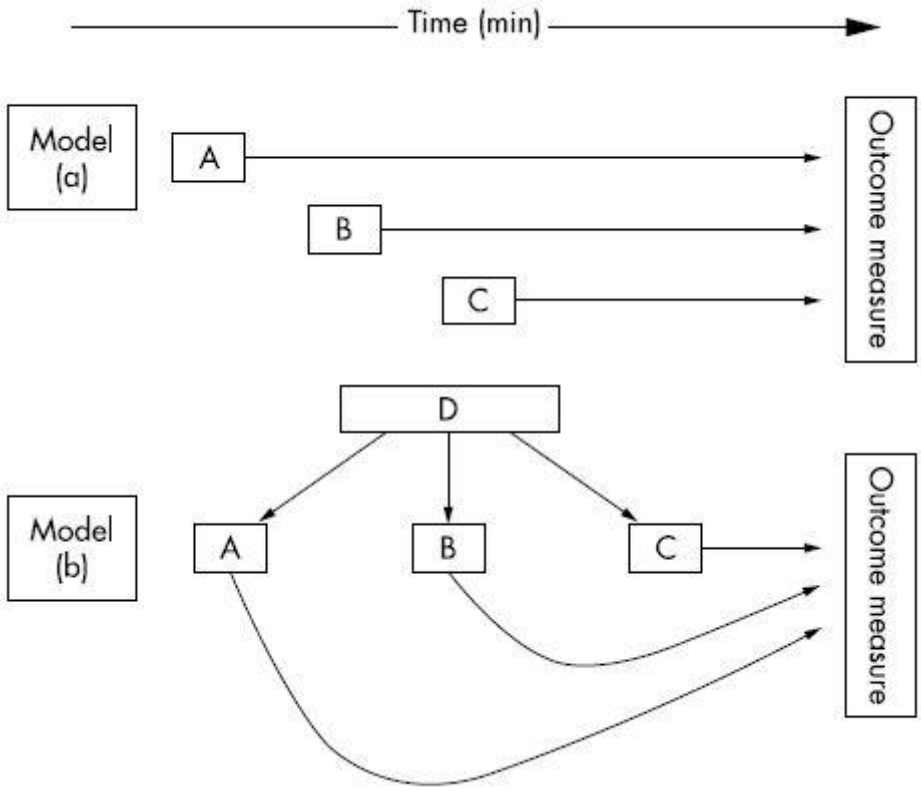


Figure 1.2. Life course accumulation models. Model (a) depicting accumulation of exposures over time to several risk factors; model (b) showing an accumulation model with risk factor clustering (after Kuh et al).[26]

The complexities inherent in teasing out effects of a risk factor recorded at multiple time points has led to a variety of statistical approaches – starting off with simple linear regressions of a risk factor with an outcome some years down the line, to more sophisticated models e.g. area under the curve or investigating the effect of different rates of change (trajectories) in risk factors.[26, 76, 77] The methods relevant to this thesis are described in more detail in the methods chapter (chapter 3).

Another important limitation of life course studies is the number of study members lost to follow up; this number of course increases the greater the duration of the study. Some of the loss is due to death and ill health (precluding participation) and it is possible that as such the analysis is biased towards healthier individuals – the so called immortal time bias.[78] However it is likely that a differential loss of participants is likely to bias to null especially given the characteristics of those attending clinic[79] and the fact that those with high (and low) BMIs in our study had increased mortality risk.[80]

Echocardiography

The history of echocardiography

Echocardiography is the ultrasound examination of the heart. The first ultrasound assessment of cardiac anatomy was made nearly 60 years ago by Elder and Hertz in Sweden in 1954.[81] In the 1960s Joyner and Reid carried out an anatomical and physiological cardiac examination,[82] while a pericardial effusion was detected on ultrasonography by Feigenbaum in the mid-sixties.[83] Echocardiographic techniques have advanced with time with each new technique being rapidly applied in clinical practice. Initially confined to M-mode, echocardiography evolved to incorporate 2-dimensional (2-D) scanning in the 1970s[84] followed by the clinical use of Doppler echocardiography towards the end of that decade.[85, 86] The 1980s saw the introduction of a number of new techniques, namely colour flow imaging,[87] tissue Doppler imaging[88] and trans-oesophageal echocardiography.[89] More recently we have had strain[90] and 3-D echocardiography[91, 92] along with the introduction of hand-held ultra-portable ultrasound machines.[93]

Echocardiographic techniques – the physics of echocardiography

Basic Physics

Echocardiography utilizes ultrasound waves which are acoustic (sound) waves with a frequency of more than 20000 Hertz. Sound waves can be defined by seven characteristics (Figure 1.3) –

Frequency – the number of cycles per second (1 cycle/second = 1 Hertz – 1 Hz)

Period – the time taken to complete 1 vibration cycle; period = 1/frequency. Period is usually measured in seconds.

Wavelength – the length of one complete cycle (measured in mm or cm or m)

Velocity – the velocity of a wave through a medium is equal to frequency X wavelength. The average velocity of sound waves in soft tissue is 1540 m/sec.

Amplitude – the maximum deviation of the wave from the cycle mean position. It is usually measured in centimetres or metres.

Power – the rate at which energy is transferred by the wave measured in Watts (W).

Intensity – the power density of the wave derived by calculating Power/Cross-sectional Area. It is measured in W/m^2.

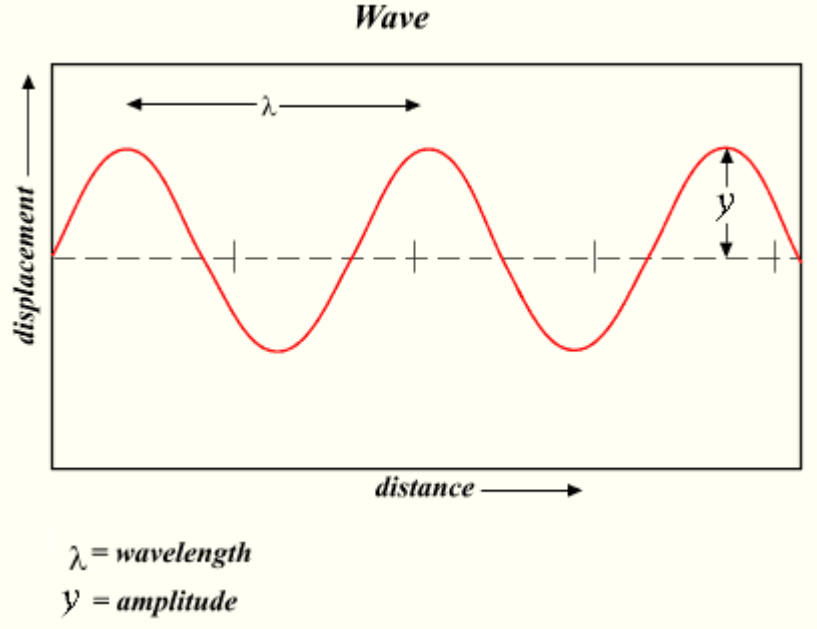


Figure 1.3. Physics of an ultrasound wave

Ultrasound imaging

Echocardiography is carried out using a transducer which produces and detects ultrasound waves (Figure 1.4). Transducers consist of piezoelectric crystals with modern transducers containing up to 3000 separate elements. When an alternating current is applied across the crystals they deform and vibrate. These vibrations give rise to the ultrasound waves by causing intermittent compression and expansion (aka rarefaction) of the transmitting medium media (gel, tissue, blood etc.). The conversion of electrical energy to mechanical energy in this way is called the "piezoelectric effect". Since crystals cannot transmit and receive simultaneously, the electrical energy is applied in brief repeated pulses to each crystal in the transducer (transmission mode) and the frequency of these pulses is termed the pulse-repetition frequency (PRF). The transmission of an ultrasound wave depends on the acoustic impedance of the transmitting medium. When the wave meets a change in impedance (e.g.

due to a change in material density) some of the energy is reflected and returns to the crystals. On receipt of the reflected wave, mechanical energy is converted into electrical energy by the transducer when it is in 'listening' mode. By measuring the time between when the ultrasound wave was sent and received, the depth of the interface giving rise to the impedance mismatch, can be estimated and an image built up.

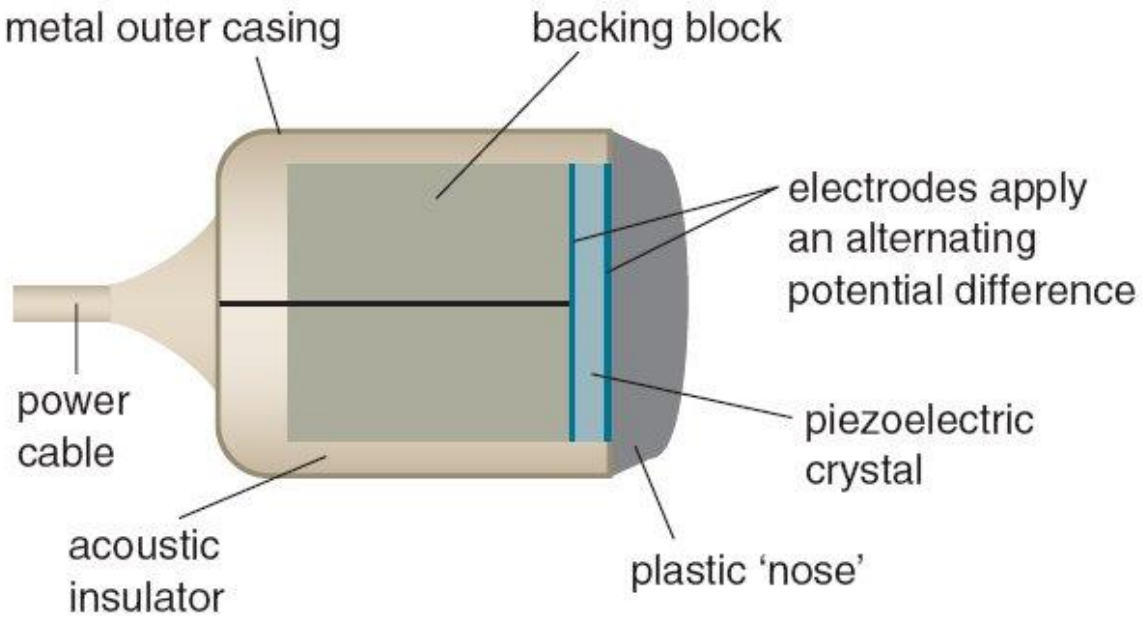


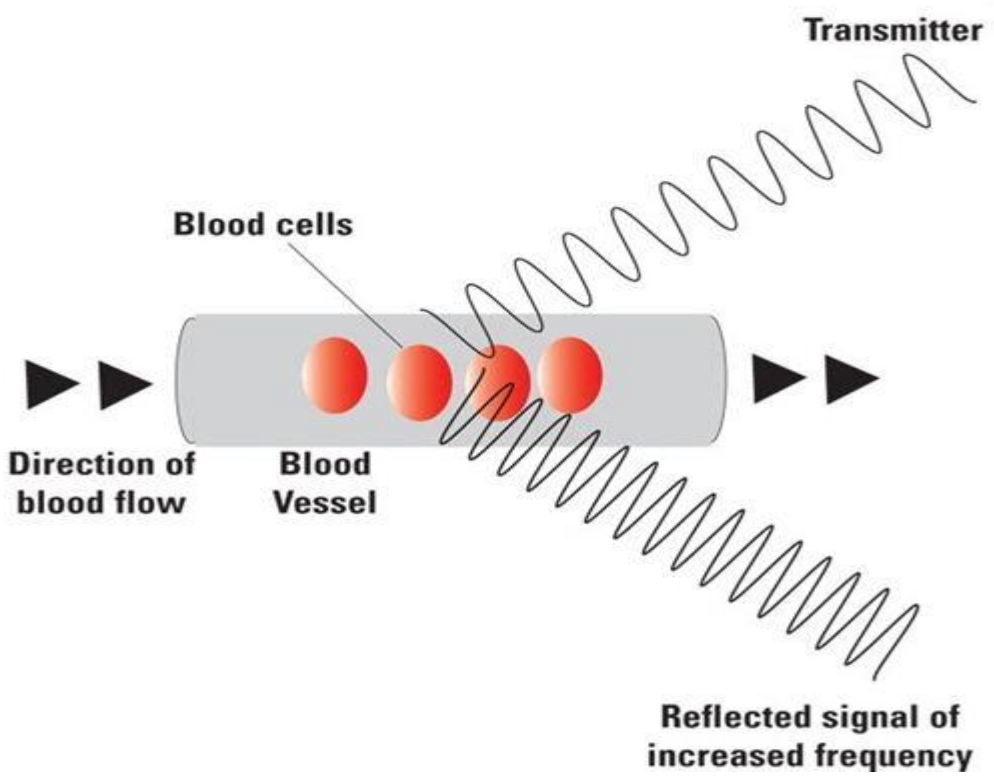
Figure 1.4. A typical transducer.[94]

In clinical practice, the transducer frequency for trans-thoracic echocardiography is typically between 2 to 2.5MHz (a higher frequency produces better resolution but has a shallower depth of penetration). Fundamental and harmonic imaging are two types of imaging that depend on the frequency of the reflected waves sent to the transducer. In fundamental

imaging the waves sent and received by the transducer are of the same frequency, whereas in harmonic imaging the frequencies of reflected waves are multiples (harmonics) of the initial wave. Harmonic imaging results in better delineation of tissue interfaces such as the endocardial border of the heart.

Doppler echocardiography

Christian Doppler first described the Doppler principle in 1842 in a paper that he presented in Prague before the Royal Bohemian Society of Sciences entitled "*Über das farbige Licht der Doppelsterne"* (Concerning the coloured light of the double stars and certain other stars of the heavens).[95-97] He explained that the pitch (analogous to frequency) of a sound was affected by motion – with the pitch rising with motion towards the listener and decreasing with movement away (Figure 1.5).



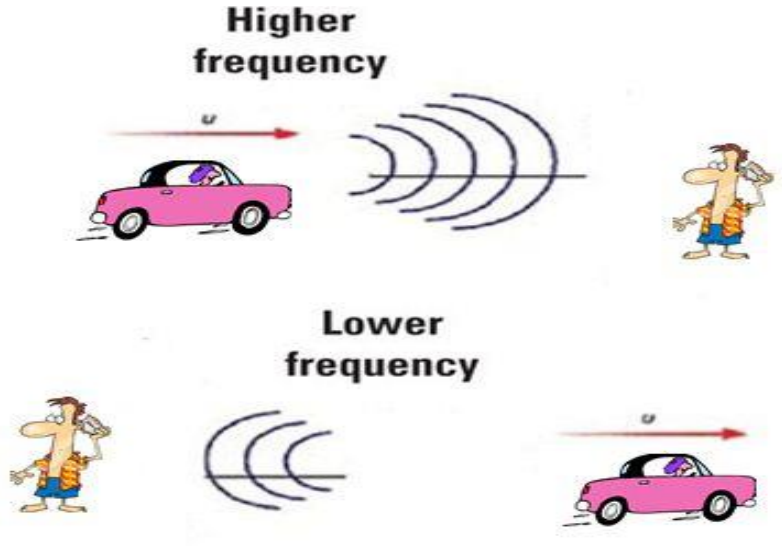


Figure 1.5. Cartoon illustrating the Doppler principle

(After Engineering Toolbox.com and The Physics Classroom)[98, 99]

This principle is applied in echocardiography when interrogating the interaction between ultrasound waves and moving red blood cells (i.e. blood flow in the heart) or moving tissue (Tissue Doppler). The *Doppler shift* is the change in frequency due to motion of the reflecting material away or towards the transducer.[100] Mathematically, the relationship of the frequency shift (ΔF) and velocity of the moving object or interface can be determined.

$$\Delta F = \frac{2 \times F_0 \times v \times cos\,\theta}{c}$$

where F_0 is the emitted frequency, v is the velocity of movement of blood towards the transducer, c is the velocity of sound in the medium and θ is the angle between the interrogating beam and blood flow (Figure 1.6).

This dependence on cos θ means that for practical purposes the angle (termed the "Doppler angle") between the interrogating beam and the blood flow must be as close to zero as possible. Usually, in the aorta angles <20^{o} can be achieved,[101] elsewhere (e.g. the carotid artery) angles <60^{o} may be considered acceptable.

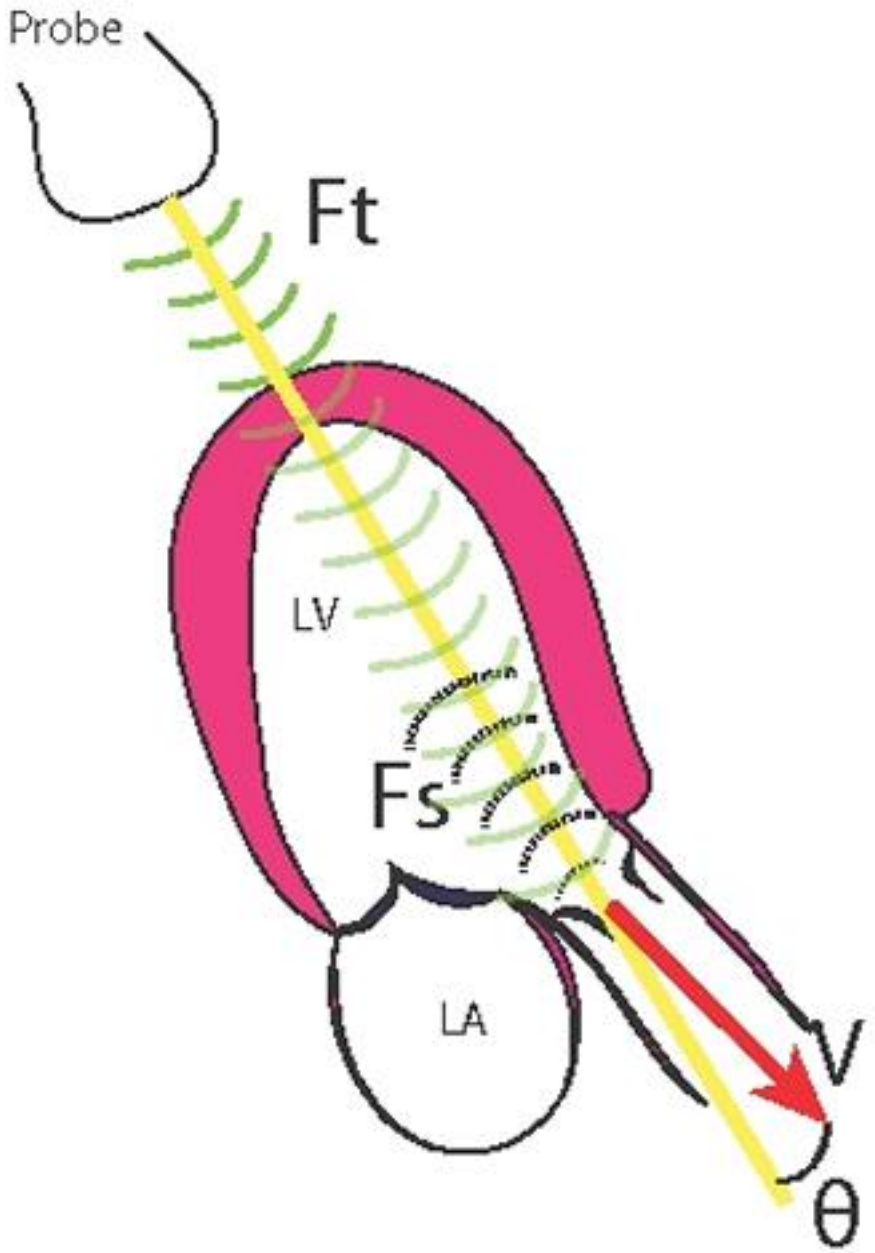


Figure 1.6. Cartoon of Doppler interrogation of blood flow through the aorta (Ft, frequency of ultrasound emitted by probe; Fs, frequency of reflected ultrasound; LV, left ventricle; LA, left atrium; Θ, the angle between the interrogating beam and blood flow) (After Kapadia et al.)[102]

There are five clinically relevant Doppler techniques – pulsed wave Doppler, continuous wave Doppler, colour flow imaging, tissue Doppler and power Doppler imaging.

Pulsed wave Doppler

Short bursts (pulses) of ultrasound are transmitted into the body. While targets at multiple points along the beam may reflect the transmitted ultrasound pulses, the probe "listens" only for a brief, fixed interval after transmission of the pulse. As a result, only signals from a specific distance are received and analysed resulting in "range resolution". Different ranges or depths can be evaluated by changing the interval between transmission of the pulse and reception of the reflected wave. A technical limitation of the pulsed Doppler technique is the maximum velocity that can be accurately resolved.[103] To accurately represent a frequency it must be sampled using a PRF at twice the frequency of interest. This is termed the *Nyquist limit*; frequencies above this limit cannot be characterised correctly as they undergo *aliasing.* With aliasing, blood flow is represented both above and below the baseline, i.e. seemingly both moving towards and away from the transducer. The upper limit of the frequency that can be detected by a given pulse is the Nyquist limit (f_{DOP}) and it is defined as half of the PRF - the number of pulses that can be transmitted from the transducer in 1 second):

$$f_{DOP} = \frac{PRF}{2}$$

Continuous wave Doppler

Instead of sending out pulses, in continuous wave Doppler there is a continuous transmission and reception of ultrasound signals. There are 2 technologies that can achieve this – some transducers have 2 distinct elements: one for transmission and one for reception; other transducers have phased array technology where one crystal is used for transmitting and the other simultaneously for receiving. Due to the lack of pulses in continuous wave Doppler, range resolution is not possible and thus it is impossible to know from where along the sample beam any recorded velocity signal arises. However, one of the advantages of continuous wave Doppler is that it does not suffer from aliasing.

Colour Flow Imaging

Colour flow imaging utilises pulsed wave Doppler techniques superimposed on a 2-dimensional or M-mode template.[104] Each pixel in the colour flow image represents a region of interest in which flow characteristics have to be measured. However doing an exhaustive velocity spectrum analysis for each pixel would be time consuming and as such only mean frequencies and variance (frequency spread) are calculated. For each pixel, the strength of the returning echo is calculated and it is painted a shade of grey based on pre-determined velocity thresholds. With repetitive sampling an average velocity and variance are calculated. A colour-reject threshold is used to display velocities above the threshold in colour, with the brightness of the colour depending on the magnitude of the velocity. Colour flow imaging does suffer from some limitations. The size of a jet of colour flow can be difficult to quantify as a 3-dimensional entity cannot be fully captured when represented in a 2-dimensional

format. As colour flow imaging utilises pulse Doppler techniques, it too suffers from aliasing and a mixing of colours when there is turbulent blood flow.

Tissue Doppler

The Doppler principle is also applied to the movement of tissue (Figure 1.7).[105] The gain and reject settings are adjusted to record the motion of the myocardium rather than the blood pool. Two things must be factored into analysis – the lower velocity of tissue compared to blood and that tissue is a stronger reflector of Doppler signal compared to blood. Once tissue velocity has been derived, displacement, strain (a measure of deformation that occurs when force is applied to tissue) and strain rate can also be calculated.[90, 106]

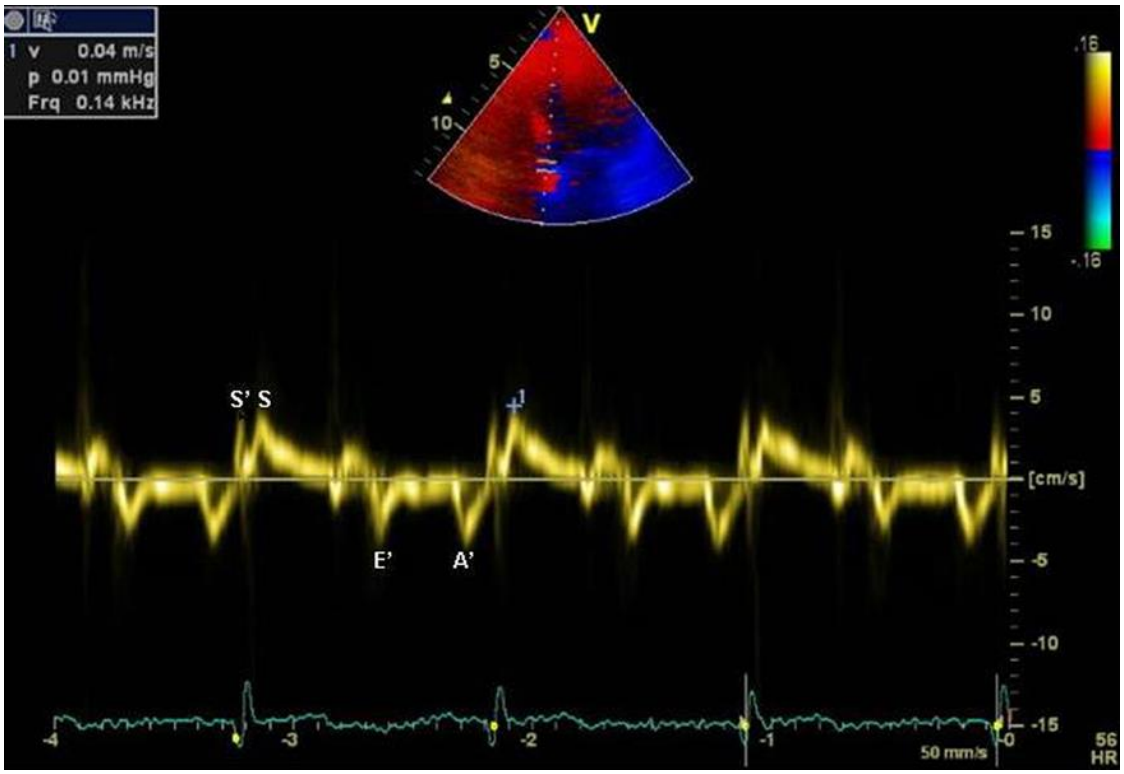


Figure 1.7. Tissue Doppler interrogation

Power Doppler

Power Doppler imaging is an additional colour flow imaging technique that overcomes some of the limitations of colour flow imaging.[107] Colour flow images are created using phase and frequency information of the autocorrelation signal created by the computer of the ultrasound machine. However amplitude of the autocorrelation signal is not used to create the colour flow image. Amplitude reflects the power of the autocorrelation signal and when it is integrated with the colour flow image a power Doppler image is produced. The most important benefit of this technique is improved flow sensitivity and a decrease in background signal noise.[108]

The role of echocardiography

Validation of accuracy

Echocardiography has revolutionised cardiology practice. After its introduction, clinicians for the first time had a tool that could offer non-invasive information on cardiac structure and function in clinic or at the bed-side. Over time, echocardiography has become the dominant imaging modality due to its portability and versatility, with its use having expanded into emergency departments, operating theatres and intensive care units where it has revolutionised practice.[109-114] Echocardiography has a long history and is well validated in being able to measure cardiac structures accurately when compared with in-vivo anatomy.[115, 116] Echocardiography has been the tool that has been used to derive normative measures of

cardiac structures and has also been validated for its use in determining haemodynamic parameters.[117-119] This has led to its integral role in delineating cardiac structure and function to aid in the management of patients with hypertension, heart muscle disease, valve disease, heart failure, congenital heart disease, arrhythmias and all forms of structural heart disease.[106, 117, 120] It is also being applied in the setting of new technologies e.g. transcatheter interventions for valve disease.[121]

Prognostic value

Information obtained through echocardiography has also been shown to have prognostic benefit. Echocardiographically determined left ventricular mass has been shown to be an independent risk factor for future cardiovascular morbidity and mortality.[122, 123] The prognostic implications of echocardiographic changes in left ventricular mass in those on anti-hypertensive treatment have also been elucidated in the literature.[124] Echocardiography has also been used for prognostic purposes in heart failure in symptomatic and asymptomatic patients with preserved or abnormal left ventricular function.[125] Echocardiography has played a key role in determining the prognosis of patients with both systolic and diastolic dysfunction,[126-131] with the prognostic value of ejection fraction also being demonstrated.[132-136] Echocardiography has played a pivotal role in determining which heart failure patients would gain a prognostic benefit from device therapy.[137, 138] It has also been used to determine cardiovascular risk[139] and prognosis post-myocardial infarction in a number of studies.[140-143] Echocardiography is the preferred measurement tool in valve lesions and has demonstrated prognostic accuracy in a variety of valvular conditions.[144, 145] Echocardiography is also a tool

in the armamentarium when determining prognosis for certain cardiomyopathic conditions[146-150] and arrhythmic processes.[151, 152]

Weaknesses

While echocardiography is a widely available, cheap and quick tool to assess cardiac structure and function, it does have its limitations. Chief among these is the fact that image quality is dependent on patient body habitus. Obesity, lung disease, deformed chest walls and breast implants all preclude optimal image acquisition. Operator skill and experience also has a role to play in obtaining images of the best quality. Reproducibility of measurements (both intra-reader and inter-reader) varies with some studies suggesting a variability of +/- 10% for ejection fraction measured by Simpson's biplane method.[153] Volume and mass measurements may be made more accurately and with better reproducibility by cardiac magnetic resonance imaging or by cardiac computed tomography scanning.[153-155] Artefact can play a role in decreasing image quality (e.g. from mechanical heart valves) and accurate haemodynamic measurements require proper alignment of the Doppler probe.[156]

Finally it must be remembered that echocardiography is a 2 or sometimes 1-dimensional representation of a 3-dimensional structure and the interpretation of images and measurements needs to be made with this in mind. 3-dimensional echocardiography is a newer technique which has recently entered clinical practice and has shown reasonably good validity against cardiac magnetic resonance.[157]

Echocardiographic measures used in this thesis

Measures of cardiac structure and function used in this thesis have been presented and critically discussed in the methods chapter (chapter 3).

Life course echocardiography

There have been few studies that have utilized echocardiography when looking at the life course influences of risk factors on future cardiac structure and function. A systematic review and meta-analysis of such studies is presented in chapter 2.

Using echocardiography in the context of a life course approach, i.e. life course echocardiography, would allow a better appreciation of the pathological consequences of earlier risk factor exposure and risk factor history on subsequent cardiac structure and function. Such improved mechanistic understanding would allow the design of appropriate trials to test the effect of earlier targeted interventions.

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Chapter 2

Cardiovascular risk factors from early life predict future adult cardiac structural and functional abnormalities: a Systematic Review of the published literature

Introduction

The evaluation of cardiovascular risk in clinical practice is based on current risk factor (RF) levels and largely disregards prior RF history and changes in RFs over the *totality* of the life course. There is considerable evidence associating RFs such as body mass index (BMI) and blood pressure (BP) in midlife with subsequent cardiovascular morbidity and mortality.[1] There is also literature cross-sectionally associating current RFs (BP and BMI) with echocardiographic changes (left ventricular mass - LVM and left ventricular hypertrophy - LVH) and with these changes relating independently to cardiovascular events.[2-4] There has also been some research relating presence or absence of diabetes to later echocardiographic outcomes.[5] However, less is known about how earlier-life levels of these RFs, changes in RFs,

and duration of and long-term control of RFs like hypertension, obesity and diabetes are associated with subsequent cardiac morphology and function as measured through echocardiography and this has never been systematically examined.[6]

Lifetime RF history can be captured by the life course approach which has been extensively used to model RF trajectories in multiple cohorts.[7] The life course approach investigates long-term biological processes that link adult health and disease risk to physical and environmental exposures occurring in gestation, childhood, adolescence, earlier in adulthood or across generations.[8] Although such an approach has not yet been widely applied to the cardiovascular domain, after initial early forays by Barker in the mid-nineties (fetal undernutrition in middle to late gestation, which leads to disproportionate fetal growth, programmes later coronary heart disease),[9] there has recently been a renewed recognition of this analytical method. This has resulted in a flurry of recent work on larger population groups, showing the far-reaching influences of early and mid-adulthood RF levels (e.g. BP) on cardiovascular morbidity and mortality many years later.[10-13] In spite of this recent utilization of a life course approach to future cardiovascular morbidity and mortality, and therefore, potentially cardiac structure and function,[13, 14] there has been less work *directly* delineating the effects of earlier RFs on future cardiac structure and function as measured through echocardiography. Elucidating these echocardiographic changes could give us better insights into the mechanisms by which early RF exposures cause future cardiovascular complications and thus enable better targeted interventions. For instance, it remains unclear whether detrimental changes in cardiac structure and function are caused by exposures or accelerated change at particularly sensitive periods in an individual's life or the overall cumulative burden of exposure. To put this in a clinical context, it is unknown, for example, whether being

overweight or being diabetic from the age of 20 years onwards is more detrimental to the heart in older age, than first becoming overweight or diabetic at the age of 50 years, or whether for individuals with the same current BP, the effect on cardiac structure and function varies depending on whether there had been a gradual increase in BP over a 30 year period or a steeper increase over a shorter period.

Using a life course approach allows us to determine whether early exposures to RFs like BP can lead to LVH in the future, although it must be borne in mind that reverse causality cannot be definitely excluded (e.g. LVH leading to hypertension) if baseline LVM is unknown (due to a lack of baseline echocardiography). However, identifying such associations remains important, as it would allow earlier targeted intervention, before the development of abnormality (e.g. LVH). Such approaches (identifying and intervening in those at greatest risk early) have been tested recently in the Danish Hypertension Prevention and TROPHY studies.[15]

Due to the lacunae thus identified in the published literature, we conducted a systematic review to determine if increasing lifetime exposure to raised BP, BMI and impaired glycaemic control was associated with worse future cardiac structure and function.

Methods

Criteria for Study Inclusion and search strategy

Studies eligible for inclusion were observational studies with *longitudinal repeated* measures of one or more of the exposures of interest (BP, BMI and glycaemic control) and *at least one*

echocardiographic examination of participants (looking at cardiac structure and/or function) in adulthood. Eligible study samples consisted of individuals who were healthy, non-disabled and community-dwelling at the time of measurement of the RFs.

Outcomes considered were any echocardiographic measure of cardiac structure (e.g. wall and chamber dimensions and volumes) or function (e.g. ejection fraction (EF), fractional shortening, E/A ratio, and tissue Doppler based measures such as E/e' ratio).

Searches of the electronic databases PubMed and EMBASE (January 1966 to December 2011) were performed using the following Mesh terms: (longitudinal OR cohort OR life course OR lifecourse OR follow up OR tracking) AND (blood pressure measurements OR body mass index measurements OR birth weight OR lipids OR glycaemic control) AND (echocardiography). Only studies in English were considered. Figure 2.1 summarises the identification of studies.

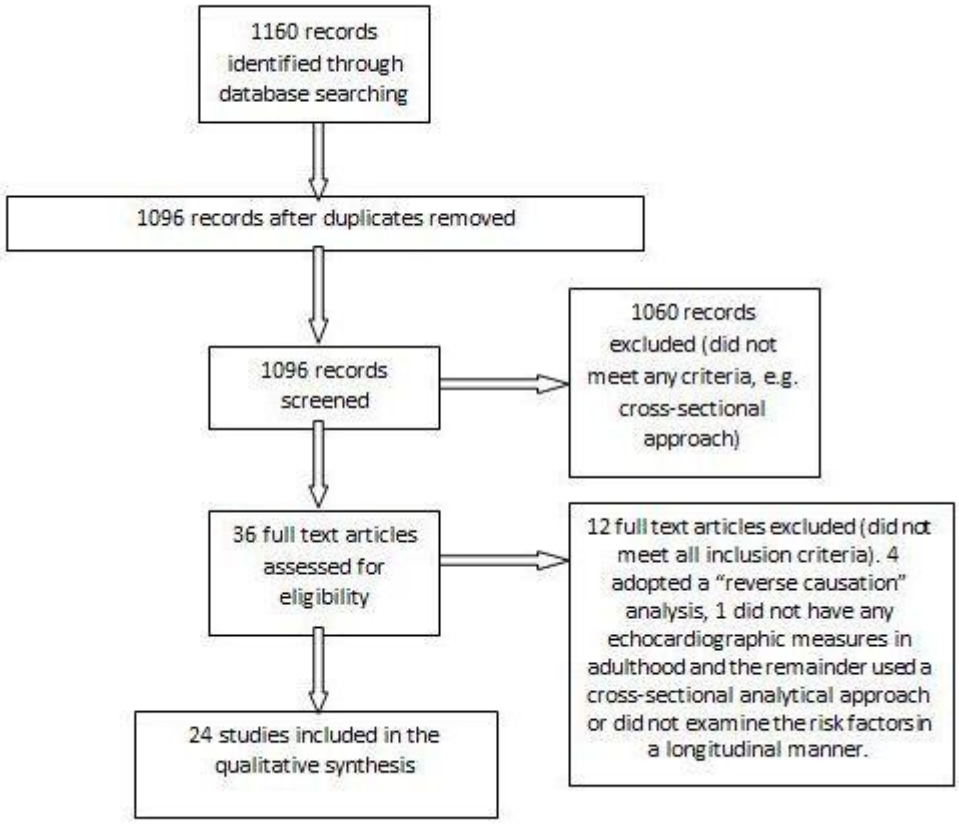


Figure 2.1. Flow of studies through the systematic review (after the PRISMA and MOOSE statements).[16, 17]

After removing duplicates, 1096 study abstracts were screened resulting in the exclusion of 1060 papers that did not meet inclusion criteria (were cross-sectional studies, hospital-based, measured outcomes other than echocardiographic parameters, or the RFs were not analysed as continuous variables). The full text of 36 articles were obtained and reviewed for eligibility using a standardised inclusion/exclusion form, and 12 were excluded as being ineligible. Of the 12 that were excluded, 4 had adopted a "reverse causation" analysis,[18-21] 1 did not have

any echocardiographic measures in adulthood[22] and the remainder used a cross-sectional analytical approach or did not examine the RFs in a longitudinal manner.[23-29]

Any uncertainty about study eligibility was resolved through discussion between my supervisors and myself. Details of relevant published results, study populations, measurement of RFs and outcomes and details of statistical analysis were extracted from the papers using a data extraction form.

The analyses presented in the papers were too varied to enable a formal meta-analysis of the published data. Furthermore, the cardiac outcomes assessed and the ages at which RFs were measured were also too heterogeneous to allow an individual level meta-analysis. Hence, no attempts were made to contact authors for additional information.

Results

The 24 papers meeting the inclusion criteria used data from 13 different cohort studies. The characteristics of included studies are provided in Table 2.1. Table 2.2 describes a summary of the associations between the RFs and the cardiac outcomes of interest. The full main findings and statistical methods used are provided in Table 2.3.

Some studies used more than one method or looked at both cardiac structure and function and have thus been included more than once in the tables.

Table 2.1. Characteristics of studies included in the systematic review

Paper: First author and year	Study name and location	Analysed sample size (at last examination round if not further qualified)	Mean Age +/- 1SD (Age range) in years at last follow up (unless otherwise mentioned)	Maximum duration of follow up in years and maximum number of repeated examination rounds for the purpose of quoted paper	Repeat measure(s) related to echocardiographic outcome for the purpose of quoted paper (not all measures may have been taken in all rounds)	Cardiac Outcome measure(s) (non-longitudinal analysis in italics)
Cardiac Structure						
Prospective approach						
Urbina[30] 1995	Bogalusa, USA	90 males and 70 females at first echocardiography round	13.3 at first echocardiography round (9-22)	4 with 1 follow-up round of echocardiography	BP, weight, height	Structure
Vasan[31] 1995	Framingham, USA	2803 men and 3411 women at baseline; 1849 men and 2152 women at 1st follow up	20-89 at baseline	8 and 1	BP, BMI	Structure
Vijayakumar[32]	Hertfordshire	290 men	66.9 +/- 3.2	70 and 2	BP, BMI, glucose and insulin	Structure

1995	Cohort, UK					
Kumaran[33] 2000	Mysore, India	435 (237 men and 198 women)	49.5 +/- 4.8	49.5 and 1	BP, BMI	Structure
Jokiniitty[34] 2001	Tampere, Finland	97 men at baseline and 86 men at follow up	35-45	10 and 1	BP, BMI	Structure
Sundstrom[35] 2001	Uppsala, Sweden	2322 men at baseline; 1221 at follow-up (475 qualified for inclusion)	70-74	20 and 1	BP, BMI, glycaemic control	Structure
Gardin[36] 2002	CARDIA, USA	5115 at baseline; 4243 at 1st follow-up; 1536 at 2nd follow-up; 1189 qualified for inclusion (544 men and 645 women)	18-30 at baseline	10 and 2	BP, BMI	Structure
Arnlov[37] 2005	Uppsala, Sweden	2330 at baseline; 1227 at follow-up (505 men qualified for inclusion)	70	20 and 1	BP, BMI, glycaemic control	Structure and function
Haji[38] 2006	Bogalusa, USA	197 men and 309 women	32 +/- 3	23 and 2 to 12 follow-ups with an average of 6	BP, BMI, fasting glucose	Structure and *function*
Strand[39] 2006	Oslo, Norway	56 men	42.1 +/- 0.5 at baseline	20 and 1	BP, BMI	Structure and *function*

Lin[40] 2007	The Longitudinal Study of Aging, China	193 at baseline; 170 at 1st follow-up; 144 at 2nd follow-up (81 men and 24 women qualified for inclusion)	71.7 +/- 3.9 (60-81)	4 and 2	BP, BMI, glycaemic control	Structure and *function*
Toprak[41] 2008	Bogalusa, USA	338 men and 486 women	36 (24-44)	24 and 1	BP, BMI, glucose	Structure
Ridderstrale[42] 2010	Military recruits, Sweden	74 male army recruits at baseline, 64 at follow-up	40	20 and 1	BP, BMI,	Structure and *function*
Accumulation or Change approach						
Johnson[43] 1983	Bourbon County, USA	837 at baseline; 77 men and 51 women qualified for final inclusion	16-19 at baseline	5 and 1	BP, BMI	Structure and function
Lauer[44] 1991	Framingham, USA	451 (152 men and 299 women)	68 +/- 6	30 and 16	BP, BMI	Structure
Zureik[45] 1995	Paris, France	177 men	51.6 +/- 2.9 (47-58)	2 and 1	BP, BMI	Structure

Bjorklund[46] 2002	Uppsala, Sweden	2322 men at baseline; 1221 at follow-up (583 qualified for inclusion)	70	20 and 1	BP	Structure and function
Gardin[36] 2002	CARDIA, USA	*Refer above*				
Lorber[47] 2003	CARDIA, USA	737 men and 881 women	18-30 at baseline	10 and 5	BP, BMI, fasting insulin levels	Structure
Li[48] 2004	Bogalusa, USA	1420 at baseline; 467 at 6th follow-up (182 men and 285 women)	32.6 (20-38)	23 and 2 to 12 follow-ups with an average of 6	BP, BMI	Structure
			Cardiac function			
Johnson[43] 1983	Bourbon County, USA	*Refer above*				
Arnlov[49] 2001	Uppsala, Sweden	2330 at baseline, 1227 at 1st follow-up (431 men qualified for inclusion)	48-51 in the 1st round	20 and 1	Glycaemic control	Function
Bjorklund[46] 2002	Uppsala, Sweden	*Refer above*				

Arnlov[37] 2005	Uppsala, Sweden	*Refer above*				
Cheng[50] 2010	Framingham Offspring, USA	1851 men and 2211 women	45 +/- 10 at baseline	16 and 4	BP, BMI, fasting glucose	Structure and function
Longitudinal modelling of cardiac outcomes						
Lieb[51] 2009	Framingham Offspring, USA	1973 men and 2244 women in long term study; 1094 men and 1511 women in short term study	45	4 to 16 and maximum of 4 follow-ups	BP, BMI, diabetic status	Structure
Cheng[50] 2010	Framingham Offspring, USA	*Refer above*				
Lam[52] 2010	Framingham Offspring, USA	1671 men and 1835 women in short term group; 2187 men and 2355 women in long term group	52+/-10 for men and 51+/-10 for women in short term group; 46+/-10 for men and 45+/-10 for women in long term group (25-74)	4 to 16 and 2-6 follow-ups	BP, BMI	Structure
McManus[53] 2010	Framingham Offspring, USA	2102 men and 2301 women in long term group; 1559 men and	45	4 to 16 and maximum of 4 follow-ups	BP, BMI, diabetic status	Structure

	1806 women in short term group

BP, Blood Pressure; BMI, Body Mass Index

Table 2.2. Associations of longitudinally analysed RFs with cardiac outcomes

Paper: First author and year	Study name and location	BP	BMI/weight	Glucose/glycaemic control	Cardiac outcome	Association with cardiac outcome
		Cardiac Structure				
Prospective approach						
Urbina[30] 1995	Bogalusa, USA	Y	Y	-	LVM	BP: +ve Weight: +ve
Vasan[31] 1995	Framingham, USA	Y	-	-	AoRD	BP: +ve for DBP and MAP, -ve for SBP and PP
Vijayakumar[32] 1995	Hertfordshire Cohort, UK	-	Y	-	LVM, IVSD, LVPWD	Weight: +ve
Kumaran[33] 2000	Mysore, India	-	Y	-	LVMI, LVH	Weight: no association
Jokiniitty[34] 2001	Tampere, Finland	Y	Y	-	LVMI	BP: +ve for PP BMI: +ve

Sundstrom[35] 2001	Uppsala, Sweden	Y	Y	-	LVH	BP: +ve BMI: +ve
Gardin[36] 2002	CARDIA, USA	Y	Y	-	LVM	BP: +ve BMI: +ve
Arnlov[37] 2005	Uppsala, Sweden	Y	Y	Y	E/A, A', LA diameter	BP: -ve for E/A, +ve for A with SBP BMI: -ve for E/A, +ve for A, +ve for LA diameter Glucose: +ve for E, +ve for A with insulin/proinsulin, +ve for LA diameter with insulin/proinsulin
Haji[38] 2006	Bogalusa, USA	Y	Y	-	LV dilation	BP: no association BMI: +ve
Strand[39] 2006	Oslo, Norway	Y	-	-	LVM, LVMI	BP: +ve for LVM with DBP BMI: +ve for LVM and LVMI

Lin[40] 2007	The Longitudinal Study of Aging, China	Y	Y	Y	LVMI, LVH	BP:+ve for LVH with PP BMI:+ve for LVMI Glucose: +ve for LVMI
Toprak[41] 2008	Bogalusa, USA	Y	Y	Y	LVH	BP: +ve for concentric LVH and DBP BMI: +ve for eccentric LVH Glucose: no association with childhood diabetes mellitus
Ridderstrale[42] 2010	Military recruits, Sweden	Y	Y	Y	LVMI	BP: +ve with MAP BMI: +ve Glucose: +ve with insulin
Accumulation or Change approach						
Johnson[43] 1983	Bourbon County, USA	Y	-	-	FS, IVSD, LVPWTD	BP: +ve with FS, IVSD, LVPWTD

Lauer[44] 1991	Framingham, USA	Y	-	-	LVMI, LVH	BP: +ve
Zureik[45] 1995	Paris, France	Y	y	-	LVMI, LVWT	BP: +ve BMI: no association
Bjorklund[46] 2002	Uppsala, Sweden	Y	-	-	LVMI, IVSD, LVPWT, EF	BP: +ve with LVMI, IVSD and LVPWT, no association with EF
Gardin[36] 2002	CARDIA, USA	*Refer above*				
Lorber[47] 2003	CARDIA, USA	Y	y	-	LVMI, LVG	BP: +ve BMI: +ve
Li[48] 2004	Bogalusa, USA	Y	Y	-	LVM	BP: +ve BMI: +ve
		Cardiac function				
Johnson[43] 1983	Bourbon County, USA	*Refer above*				
Arnlov[49]	Uppsala, Sweden	-	-	Y	EF	Glucose: -ve

2001							
Bjorklund[46]	Uppsala, Sweden	*Refer above*					
2002							
Arnlov[37]	Uppsala, Sweden	*Refer above*					
2005							
Cheng[50]	Framingham Offspring, USA	Y	Y	Y	LVIDD, LVWT, FS	BP: +ve for LVIDD, LVWT and FS with SBP and PP, -ve for FS and LVIDD with DBP BMI: +ve for LVIDD and LVWT Glucose: Individuals with diabetes mellitus experienced greater age-associated increases in LVWT and lesser decrease in LVIDD (see table 3 for details)
2010							

Longitudinal modelling of cardiac outcomes						
Lieb[51] 2009	Framingham Offspring, USA	Y	Y	Y	LVM	BP: +ve BMI: +ve Glucose: Subjects in low RF group experienced lesser increases in LVM with time (see table 3 for details)
Cheng[50] 2010	Framingham Offspring, USA	*Refer above*				
Lam[52] 2010	Framingham Offspring, USA	Y	Y	-	AoRD	BP: +ve for AoRD with DBP and PP, -ve for AoRD with SBP and MAP BMI: +ve
McManus[53] 2010	Framingham Offspring, USA	Y	Y	-	LA diameter	BP: +ve for LA diameter with SBP, -ve for LA diameter with

		DBP BMI: +ve

BP, blood pressure; BMI, body mass index; LVM, left ventricular mass; AoRD, aortic root diameter; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; PP, pulse pressure; IVSD, interventricular septal thickness in diastole; LVPWD, left ventricular posterior wall thickness in diastole; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; LA, left atrium; LV, left ventricle; FS, fractional shortening; LVPWT, left ventricular posterior wall thickness; LVG, left ventricular geometry; EF, ejection fraction; LVIDD, left ventricular internal diameter in diastole; LVWT, left ventricular wall thickness

Table 2.3. Main findings and statistical methods used

Paper: First author and year	Study name and location	Main findings	Statistical methods used
		Cardiac Structure	
Prospective approach			
Urbina[30] 1995	Bogalusa, USA	BP: Higher SBP and DBP at the time of first examination (average age of 13.3 years, age range 9 to 22 years) predicted higher LVM at follow-up 4 years later. Weight: Higher adiposity (weight, ponderal index, triceps skin fold thickness) at first examination predicted higher LVM at follow up in univariable analyses. In multivariable analyses only baseline weight was significant in determining final LVM consistently across both sexes.	ANOVA used to look at sex and race differences and interactions. Tracking coefficients for anthropometric measures, BP and LVM by sex derived and colinearity tested for.
Vasan[31] 1995	Framingham, USA	BP: AoRD in individuals aged 20to 89 years positively associated with MAP and DBP and inversely associated with PP and SBP. Incorporating BP measured 8 years previously in the models yielded minimal changes in r^2. BMI: Analysed in cross-sectional manner.	Initially univariable regression analyses carried out determining correlation coefficients for the RF variables with AoRD as the dependent variable. Multivariable regression analyses then carried out.
Vijayakumar[32] 1995	Hertfordshire Cohort, UK	Weight: Higher weight at 1 year associated with lower LVM at a mean age of 66.9 years, after adjustment for confounding factors. Higher weight at 1 year positively associated with IVSD, LVPWD and RWT but not with	Multiple regression analysis relating weight at 1 year to LVMI adjusted for adult BSA, SBP and age.

		LVIDD, LVIDS and cardiac output before and after adjustment for BSA. Higher birth weight non-significantly associated with decreasing LVM.	
Kumaran[33] 2000	Mysore, India	Weight: Birth weight (when adjusted for sex) was not associated with LVMI or with LVH at a mean age of 49.5 years. Longer length at birth length was associated with increasing LVMI, LVH and RWT.	Linear regression and logistic regression relating birth size measures to LVM and LVH, respectively.
Jokiniitty[34] 2001	Tampere, Finland	BP: Baseline 24h PP in 35 to 45 year old men positively associated with LVMI 10 years hence. PP stronger predictor of future LVMI than SBP or DBP. Increase in PP over the 10 year period correlated with increase in LVMI. BMI: The best predictive model for increase in future LVMI included increasing BMI.	5 clusters of baseline BP variables chosen – casual BP, daytime IAMB, nocturnal IAMB, 24h IAMB and a 5th cluster with all preceding BP variables. Stepwise regression analyses performed to identify models predictive of future LVMI.
Sundstrom[35] 2001	Uppsala, Sweden	BP: High SBP and DBP at age 50 years predicted prevalence of LVH 20 years later. BMI: High BMI at age 50 years predicted increased prevalence of LVH 20 years later Glycaemic control: Analysed in cross-sectional manner.	Multiple logistic regression used to adjust for RFs which were treated as dichotomous variables. ANOVA used to calculate differences in means amongst 4 LVG groups.
Gardin[36] 2002	CARDIA	BP: In a biracial population 28 to 40 years of age, initial SBP significantly positively associated with year 10 LVM in white men and black women and change in SBP positively associated with future LVM in black women.	Bivariable Pearson correlation coefficients computed for change in LVM and each RF. Multiple linear regression used to estimate effect of each RF.

		BMI: Baseline BMI and change in BMI significant positive predictors of 10 year future LVM.	
Arnlov[37] 2005	Uppsala, Sweden	BP: Higher SBP and DBP at age 50 years associated with decreased E/A ratio after adjustment at age 70 years. Higher SBP associated with higher A-wave, but no association with DBP. No association between either SBP or DBP and LAD. BMI: Higher BMI at age 50 years was associated with decreased E/A ratio and increased A-wave after adjustment. Higher BMI at age 50 years associated with greater LAD at age 70 years. Glycaemic control: E-wave at age 70 years positively correlated to fasting glucose at age 50 years. A-wave at age 70 years positively correlated to specific insulin and proinsulin levels at age 50 years. LAD at age 70 years positively correlated to specific insulin and proinsulin levels at age 50 years.	RFs measured at age 50 years related to echocardiography measures at 70 years using partial correlation coefficients.
Haji[38] 2006	Bogalusa, USA	BP: Childhood BP (mean age 11 +/-3 years) not associated with adult LV dilation (mean age 32 +/-3 years). BMI: BMI in childhood positively predicted LV dilation in adulthood. Cardiac function analysed in cross-sectional manner.	RFs measured at first and last examinations used as the childhood and adulthood values. Multiple logistic regression used with RFs corrected for age, gender and race.

Strand[39] 2006	Oslo, Norway	BP: Baseline DBP in men aged 42.1 +/- 0.5 years positively predicted LVM 20 years in the future. SBP was not associated with future LVM. BMI: Baseline BMI positively predicted LVM and LVMI 20 years in the future. Cardiac function related to subgroups only.	Univariable regression analysis followed by multivariable linear regression analysis.
Lin[40] 2007	The Longitudinal Study of Aging, China	BP: Baseline PP positively associated with year 4 LVH in a univariable model in individuals with a baseline age of 71.7 +/-3.9 years. BMI: Baseline BMI positively associated with year 4 LVMI in a univariable model. Glycaemic control: Baseline fasting glucose positively correlated with year 4 LVMI. Cardiac function analysed in cross-sectional manner.	Univariable analysis initially carried out followed by stepwise multiple regression.
Toprak[41] 2008	Bogalusa, USA	BP: DBP levels in childhood (5 to 18 years, average age 12 years) significant positive predictor of concentric LVH in adulthood (24 to 44 years, average age 36 years, 24 years after childhood examinations) BMI: Higher BMI in adulthood and childhood significant determinants of developing eccentric LVH. Glycaemic control: Childhood diabetes mellitus was not associated with adult cardiac structure.	ANCOVA was used to evaluate differences between 4 LVG groups. Adjusted multinomial logistic regression analyses performed to define adult and childhood determinants of LVG in adulthood.

Ridderstrale[42] 2010	Military recruits, Sweden	BP: MAP at age 20 years positively associated with LVMI at age 40 years. BMI: Baseline BMI positively associated with follow-up LVMI in a univariable model. Glycaemic control: Baseline insulin levels positively related to follow-up LVMI in those with elevated baseline BP in multivariable model Cardiac function analysed in cross-sectional manner.	Longitudinal changes in RFs analysed using two-way ANOVA. RFs related to later LVMI by linear and regression.
Accumulation or Change approach			
Johnson[43] 1983	Bourbon County, USA	BP: Higher sustained 5 year SBP between 16-19 years and 21-24 years (follow-up measures used but due to high tracking and selection carried out this can be	BP measured at baseline (16 to 19 years) and selected sample (those above 95th, below 5th percentile of SBP at baseline and a random sample of the rest) measured again

		interpreted as sustained high SBP) associated with higher FS and mean velocity of circumferential fibre shortening. IVSD, LVPWTD and LVPWTS significantly less in those with sustained low SBP versus those in intermediate and higher SBP groups. LVIDD and LVIDS did not differ among groups. BMI: Measures of body size used as correcting factors in the analyses.	5 years later. High, intermediate and low SBP groups defined in terms of follow-up SBP and ANOVA used to compare echocardiography measures across the three groups.
Lauer[44] 1991	Framingham, USA	BP: Higher 30 year average SBP positively associated with LVMI and LVH at follow-up (average age of 68 +/- 6 years). 30 year average DBP correlated with LVMI but to a lesser extent than SBP. BMI: Analysed in cross-sectional manner.	Student's t test and Pearson correlation coefficients used to estimate associations between RFs and LVM. Multivariable linear regression analyses carried out.
Zureik[45] 1995	Paris, France	BP: 2 year increases in SBP and DBP associated with increases in LVMI and LVWT in men aged 51.6 +/- 2.9 years at baseline. BMI: 2 year BMI changes not associated with change in LV measurements.	Changes in baseline and follow up values assessed using Student's t tests. Pearson correlation coefficients used in univariable analysis and multiple linear regression in multivariable analysis.
Bjorklund[46] 2002	Uppsala, Sweden	BP: IVSD, LVPWT, LVMI at age 70 years increased in those with sustained hypertension over previous 20 years. EF not associated with BP.	Logarithmic transformation for skewed variables. ANOVA used to calculate differences in means; potential confounders taken into account by ANCOVA.
Gardin[36] 2002	CARDIA	*Refer above*	

Lorber[47] 2003	CARDIA	BP: In a biracial population 28 to 40 years of age, black men and black women with increasing SBP over 10 years had higher LVMI at 10 year follow-up. For black women the same was true for LVG. BMI: Black men, black women and white women with increasing BMI over 10 years had higher LVMI. Glycaemic control: Analysed in cross-sectional manner.	10 year trends in BMI and BP assessed with year 10 LVM and LVG by fitting for SBP and BMI a separate regression line to the 10 year follow-up for each person and calculating Pearson correlation coefficients between the person-specific slopes estimated from regression models and LVMI and LVG. A linear random coefficients model was used to obtain the person-specific slopes.
Li[48] 2004	Bogalusa, USA	BP: Higher SBP in childhood and greater cumulative burden from childhood to adulthood (AUC over a 23 year period) associated with higher LVM at an average age of 32.6 years (age range 20-38 years). BMI: Higher BMI in childhood and greater cumulative burden from childhood to adulthood (AUC) associated with higher LVM at 23 year follow-up.	Multiple regression with LVM as outcome and standardized risk factor measures since childhood and AUC of risk factors as explanatory variables.
		Cardiac Function	
Johnson[43] 1983	Bourbon County, USA	*Refer above*	

Arnlov[49] 2001	Uppsala, Sweden	Glycaemic control: Fasting glucose at age 50 years was negatively correlated with EF at 70 years.	As for Arnlov et al 2005
Bjorklund[46] 2002	Uppsala, Sweden	*Refer above*	
Arnlov[37] 2005	Uppsala, Sweden	*Refer above*	
Cheng[50] 2010	Framingham Offspring, USA	BP: In individuals with a mean age of 45 +/- 10 years, higher SBP, PP and hypertension treatment significantly related to both greater LVIDD and LVWT . SBP and PP positively associated with FS; DBP negatively associated with FS and LVIDD. BMI: Higher BMI significantly related to both greater LVIDD and LVWT. Glycaemic control: Individuals with diabetes mellitus experienced greater age-associated increases in LVWT and lesser decrease in LVIDD. Individuals in low RF group experienced greater changes in FS with age compared to those in high RF group.	Long term changes: Multilevel models used to model individual changes in LVM with age over a 16 year period. Short term change: Four year echocardiographic changes between exams 4-5 and exams 5-6. RFs used from earliest of each consecutive pair of exams. Generalised estimating equations used to allow for fact that some participants contribute twice. To estimate the "overall burden" of RFs, high risk and low risk groups were created (based on presence/absence of hypertension, obesity and diabetes). Median SBP and DBP among the groups used in the regression equation.

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Lieb[51] 2009	Framingham Offspring, USA	BP: In individuals with a mean age of 45 years, increase in SBP was associated with increase in LVMI. BMI: Increasing BMI associated with greater increments in LVM; association stronger in women. Glycaemic control: Subjects in low RF group experienced lesser increases in LVM with time.	As for Cheng et al 2010
Cheng[50] 2010	Framingham Offspring, USA	*Refer above*	
Lam[52] 2010	Framingham Offspring, USA	BP: In individuals with average ages of 52+/-10 years for men and 51+/-10 years for women in short term group and 46+/-10 years for men and 45+/-10 years for women in long term group (age range 25-74 years), lower SBP and higher DBP associated with greater AoRD in mutually adjusted short term change models, also adjusted for BMI, age and sex. In similar models with PP and MAP replacing SBP and DBP, lower PP and higher MAP associated with greater AoRD. In long term change models including the same variables, higher DBP was associated with greater AoRD and lower SBP with greater AoRD in men.	As for Cheng et al 2010

		In similar models with PP and MAP replacing SBP and DBP, lower PP and higher MAP associated with greater AoRD. BMI: Higher BMI associated with greater AoRD in short and long term change analyses after adjustment for BP, age and sex.	
McManus[53] 2010	Framingham Offspring, USA	BP: In individuals with an average age of 45 years, participants with higher RF burden (higher SBP) had a greater LAD increase after 16 years. DBP was inversely related to LAD size. BMI: Participants with a higher RF burden (higher BMI) had a greater LAD increase after 16 years. Glycaemic control: Analysed in cross-sectional manner.	As for Cheng et al 2010

LVM, Left Ventricular Mass; IVSD, Interventricular septal diameter; LVPWD, Left ventricular posterior wall diameter; RWT, Relative wall thickness; LVIDD, Left ventricular internal diameter in diastole; LVIDS, Left ventricular internal diameter in systole; BSA, Body Surface Area; LVMI, Left ventricular mass index; SBP, Systolic blood pressure; LVH, Left ventricular hypertrophy; BP, Blood pressure; LVPWTD, Left ventricular posterior wall thickness in diastole; LVPWTS, Left ventricular posterior wall thickness in systole; ANOVA, Analysis of variance; BMI, Body mass index; AUC, Area Under the Curve; LV, Left ventricle; RF, Risk factor; DBP, Diastolic blood pressure; LVG, Left ventricular geometry; MAP, Mean arterial pressure; PP, Pulse pressure; LVWT, Left ventricular wall thickness; FS, Fractional shortening; AoRD, Aortic root diameter; LAD, Left atrial diameter; IAMB, Intra-arterial ambulatory blood pressure; EF, Ejection Fraction; ANCOVA, Analysis of covariance

There was more than 1 paper from 5 studies; Framingham (2 papers), Framingham Offspring (4), Bogalusa (4), Uppsala (4) and CARDIA (2). These papers focussed on different RFs and/or outcomes and were thus all included in the review. The range of follow up periods in these studies was wide, varying from 2 years to 70 years and the mean age of study members at baseline varied from 7 years to 89 years. Most studies were conducted in adult participants, although 4 measured RFs in children with follow up into adulthood (Bogalusa, Hertfordshire cohort and the studies by Johnson and Kumaran).[32, 33, 41, 43] Six studies were in men only (Uppsala cohort studies and in the studies by Ridderstrale, Vijayakumar, Jokiniitty, Strand and Zureik),[32, 34, 35, 37, 39, 42, 45, 46, 49] but the majority had male and female participants. Bogalusa and CARDIA had a purposely bi-ethnic study population, while Kumaran's study was on South Asian Indians and Lin's study on Chinese seniors. The others consisted of European-origin population cohorts.

The longitudinal relationship between RFs and future cardiac structure and function was investigated in a variety of ways. Papers from the same study sometimes used different approaches while more than one approach was also used in the same paper. Although there was some overlap, we have divided the studies into 3 broad groups (depending on the approach to data analysis).

One group of studies related RFs at a single point in time with cardiac structure measured at a subsequent time point: [2, 30, 33-42] we have called this the "*prospective approach*" for the purposes of this review. The second group of studies, with regularly repeated measures of RFs, calculated summary measures of the RFs over a period of time for each individual, e.g. the area under the curve (AUC) or rate of change, and related those to future cardiac structure and function.[30, 44, 46-48] We have labelled this an "*accumulation or change approach*". One

study fell into both the “prospective” and “accumulation or change” categories as it carried out both types of analysis in the same paper.[36]

A third approach, used only in the Framingham Offspring papers, concentrated on investigating the short term changes in RFs with concurrent changes in cardiac measures.[50-53] These studies also investigated the associations between baseline RFs and subsequent longitudinal changes in cardiac measures over a longer period of time; an approach which did not strictly fit our inclusion criteria as it did not utilise repeated measures of the RF and also looked at longitudinal change in the *outcome* measure rather than in the RF. However, given the similarity of approach we have included these studies in this review for comparative purposes. We have called this approach “*longitudinal modelling of cardiac outcomes*”. This category is dealt with at the end of the results in a separate section.

Within each of these categories, results from studies with younger participants have been presented first followed by studies with older patients.

Cardiac structure

Blood pressure

The relationship between BP and cardiac structure was investigated in all 13 cohorts.

“Prospective approach”

BP measured at different times across the lifetime has been positively related to subsequent left ventricular (LV) wall thickness and mass.

Childhood Systolic and Diastolic BP (SBP and DBP) (average age 13.3 years) were positively associated with LVM measured 4 years later and LVH measured 19 years later in Bogalusa, but SBP was not associated with LV dilation 19 years later. [30, 38, 41] Similar positive associations between SBP and mean arterial pressure (MAP) measured in childhood and adolescence and future LVM (measured 10-20 years later) were observed in young adults (18-30 years in age). [36, 42] These studies did not investigate the role of current BP in these associations.

Vasan found that previous BP did not provide additional information when current BP was known when predicting aortic root diameter in a population ranging from 20 years to 89 years in age.[31]

The association between SBP at older ages and subsequent cardiac structure was considered in 4 studies. In one study SBP and DBP at age 50 years were associated with an increased prevalence of LVH at age 70 years,[35] while in another, DBP at age 42.1 years positively predicted LVM 20 years later.[39] In a study of elderly Chinese, only baseline pulse pressure (PP) was positively associated with LVH 4 years later.[40]

"Accumulation or change approach"

Studies have generally shown a relationship between faster rates of SBP change and higher cumulative SBP across the life course and poorer cardiac structure.

Greater LVM at age 33 years was associated with a greater cumulative SBP burden over the prior 23 year period (quantified by AUC),[48] while greater wall thickness [(interventricular septal thickness in diastole (IVSD) and left ventricular posterior wall thickness in diastole (LVPWT)] but not left ventricular internal diameter in diastole (LVIDD) in 21 to 24 year olds was associated with sustained higher BP over the preceding 5 years. [43]

In young black men and black women, a greater increase in SBP over 10 years was positively associated with future LVM index (LVMI).[47]

Similarly, in older samples, greater wall thickness was associated with sustained hypertension in Uppsala (50 years at baseline, 20 year follow up)[46] and faster increases in SBP in a Parisian cohort (47-58 years at baseline, 2 year follow up).[45]

In the Framingham cohort, average 30-year SBP was calculated which positively correlated with LVMI and LVH at follow up when individuals were aged 68 years.[44]

BMI and weight

"Prospective approach"

The relationship between weight at birth or in infancy with later cardiac structure was investigated in 2 studies. Birth weight was not associated with LVMI or left ventricular geometry (LVG) at a mean age of 49.5 years, and a longer length at birth showed a weak and non-significant association with increasing LVMI, LVG and relative wall thickness (RWT).[33] However, in the study with the longest follow-up, greater weight at 1 year was associated with lower LVM, IVSD, LVPWT and RWT, but was not associated with LVIDD at a mean age of 70 years.[32]

Higher BMI or weight in children and young adolescents was related to greater future LVM,[30] LV dilation, eccentric LVH and left atrial diameter (4 years later).[38, 41] BMI in young adults was also positively associated with LVM 10 and 20 years later.[36, 42]

BMI was related to cardiac structure in 3 older cohorts where it was predictive of future LVMI after 4, 10 and 20 years respectively (baseline ages 35-45, 71.7 and 42 years respectively).[34, 39, 40] High BMI at the age of 50 years was also associated with increased prevalence of LVH and higher left atrial diameter at 70 years.[35, 37]

"RF accumulation or change approach"

Only 3 studies have related summary measures of repeated BMI to cardiac structure. A greater cumulative BMI burden (AUC) over a period of 23 years was associated with a higher LVM at 33 years.[48] Among black men and black and white women, greater increases in BMI over a 10 year period, were associated with a greater LVMI at ages 28-40 years.[36]

In older individuals (52 year old men), BMI changes were not associated with changes in LV structure. However the follow up was only for 2 years.[45]

Glycaemic control

All studies considering glycaemic control took a "prospective" approach. Although no relationships between childhood glycaemic control and later cardiac structure were evident from the analyses, this was not the case for measures of glycaemia in adult life.

Only 4 studies considered the prospective effect of glycaemic control on cardiac structure.[37, 40-42] Fasting glucose measured in childhood was not associated with LVH 24 years later.[41] However in 20 year olds, baseline insulin levels were associated with LVMI measured 20 years subsequently.

Relationships between glycaemic control and cardiac structure were evident in older cohorts. Proinsulin levels at age 50 years were positively correlated with left atrial diameter at age 70 years,[37] while fasting glucose at baseline was positively correlated with year 4 LVMI in Chinese seniors.[40]

Longitudinal modelling of cardiac outcomes

The Framingham Offspring Study papers have concentrated on relating baseline RFs to longitudinal changes in cardiac measures over 4 year and 16 year periods.[50-53] Multilevel modelling was used to evaluate the correlates of LVM prospectively over a 4-16 year period.

Higher baseline SBP was associated with greater increases in LVMI, and higher SBP and PP were significantly related to greater increases in LV dimensions and wall thickness as well as larger increases in left atrial diameter.[51] The relationships between BP and change in aortic root diameter were more complex with lower baseline SBP and PP and higher baseline DBP and MAP being associated with greater increases in follow-up aortic root diameter.[53]

Baseline BMI was also related to changes in cardiac structure with positive associations with increases in LVIDD, LV wall thickness[50] and LVM, the last association being stronger in women.[51] Higher BMI was also positively associated with a greater increase in aortic root diameter.[52]

Cardiac function

There were a limited number of studies investigating the effect of RFs on cardiac function. In general the studies did find that BP, BMI and glycaemic control were all predictors of future cardiac function.

A total of 9 studies investigated cardiac function of which 4 were excluded from this section as analyses were carried out in a cross-sectional manner or only on a subgroup of the study cohort.[38-40, 42] Of the 5 papers investigating longitudinal associations, 3 were on the Uppsala cohort.[37, 43, 46, 49, 50] All studies considered BP and only the Uppsala group investigated BMI and glycaemic control.

Sustained higher SBP over a 5 year period in adolescents and young adults was positively associated with fractional shortening and mean velocity of circumferential fibre shortening, measured at 21-24 years.[43] In the Framingham Offspring cohort, higher baseline SBP was associated with faster increases in fractional shortening.[50] In older samples, although BP did not show a relationship with EF, higher SBP and DBP at age 50 years were associated with decreased E/A ratio and higher SBP to higher A-wave 20 years later.[37, 46]

In the Uppsala cohort, higher BMI at age 50 was associated with diastolic dysfunction manifest as decreased E/A ratio and larger A-wave after adjustment at age 70.[37] Fasting glucose at 50 years was negatively related to EF at age 70, and positively correlated with E-wave,[49] and specific insulin and proinsulin levels were positively correlated with the magnitude of the A-wave.[37]

Discussion

Most studies included in the review show associations between higher SBP and BMI at an earlier time-point and poorer cardiac structure measured up to 70 years later. Single measures of SBP and BMI measured in childhood, adolescence and early adulthood and greater cumulative burden of these RFs predict cardiac measures (LVM, LV wall thickness) in adulthood in the few studies that look at this. Overall, there was a lack of studies relating birth weight, infant weight or glycaemic control to cardiac structure and a lack of studies considering the longitudinal relationship of RFs with cardiac function.

Assessment of bias and justification for exclusions

Due to the variation in cardiac measures investigated (even for a single cardiac measure such as LVM, indexing was done in a variety of ways), the variation in age at measurement of RFs and length of follow-up, and the differences in statistical analysis with different levels of adjustment for potential confounding variables, it was not possible to perform a meta-analysis of results. We were thus also unable to formally assess publication bias. By systematically reviewing the literature according to published guidelines[16, 17] and following a pre-specified protocol, we have attempted to include all published results of the main associations of interest. However, we did limit our search to two electronic databases using the Mesh terms stated above and to studies written in English, and therefore, may have missed some relevant studies.

Interpretation of the findings

Ideally, life course studies require RFs to be collected over a substantial period of time and at various phases of the life course. The studies that have shown single RF measurements in childhood, adolescence or early adulthood to be correlated with adult echocardiographic measures may reflect "tracking" of the RF from childhood to adulthood (those with high levels of a RF in childhood continue to have high levels in adulthood).[54] Few studies investigate this possibility and so it remains unclear whether these observations can be interpreted as showing a distinct contribution from earlier exposure to RFs. Current SBP seemed to account for the effect of SBP measured 8 years earlier in the only study that investigated whether prior SBP had a predictive value independent of current SBP.[31] The question of whether SBP measured earlier in the life course has an independent role (by affecting cardiac measures in a particularly sensitive period of the life course) remains unclear.

Other studies suggest a "cumulative" effect of exposure to obesity and hypertension on later echocardiographic results, possibly through an accrual of damage over time worsened by prolonged exposure. However, no study has analysed the impact of RF trajectories starting from birth and continuing to early, mid and later adulthood on cardiac structure and function at an older age. Neither of the two studies investigating very early weight and adult LVM found evidence of an association, suggesting that fetal development associated with low birth weight in the normal range exerts minimal effect on future LVH. However, both studies were quite small and may have lacked the required statistical power to detect a relatively small relationship.

While this review focuses on the effect of long-term and longitudinal changes in BP, BMI and glycaemic control on cardiac structure and function, the possibility of reverse causality cannot be ruled out in those studies without baseline echocardiography. Some studies have explored the effects of an echocardiographic diagnosis such as LVH on subsequent levels of BP. These studies have shown that increased LVM, in normotensive individuals or subjects with optimally controlled blood pressure, predicts the development of future hypertension.[18, 21] Poorer baseline cardiac function in the form of lower EF has also been found to be associated with subsequent higher SBP.[19]

Some studies suggest that 24 hour PP, as opposed to SBP, is more predictive of later LVM.[34] Different BP parameters (SBP, DBP, PP, MAP) reflect the effect of BP in subtly different ways. For example, PP depends on stroke volume and arterial stiffness whereas MAP is determined by cardiac output and peripheral resistance.[55, 56] From the papers reviewed, it is not possible to determine which measures are the most useful predictors over the longer term, as different measures have not been compared against each other. Consideration of these multiple BP measurements in future longitudinal studies may result in better insights into the hemodynamic mechanisms acting over the life course to affect cardiac structure and function.

The studies in our review showed associations between poorer glycaemic control and worse left ventricular mass, ejection fraction and E/A ratio.[37, 40-42] However caution would be needed before extrapolating these findings to all population groups due to the small number of studies. In addition, the effect of *long-term* glycaemic control was not measured and although

attempts were made to account for the role of confounding factors, it is difficult to tease out the effect of glycaemia independent of its effect through BMI.

Implications of the findings

One of our striking findings was the lack of a standardised approach to analysis. The papers in this review were published between 1983 and 2010, and the analytical approaches have developed in line with the changing nature of the hypotheses with regard to biological mechanisms. Multivariable linear regression, relating the RF at a single time point to a subsequent echocardiographic measure, has been used in most studies. However, analyses become more complex if the aim is to use repeated measures of the RF. A few studies have attempted to deal with problems of modelling correlated measures of exposure by creating a summary measure for each individual e.g. AUC, or rate of change,[57] and relating these to the outcome.[44] However, no studies have as yet attempted to disentangle the effect of "cumulative" RF burden from exposures during sensitive periods.[58, 59] In the domain of life course epidemiology and life course cardiology in particular, there is no standard statistical approach to analysis linking a repeated exposure to a subsequent health outcome. The most appropriate method will depend on the specific hypothesis under study and hence the plurality of techniques used in the included papers.[60]

Another issue is the added complexity when children are followed up into early adulthood as childhood growth may not be adequately captured by changes in childhood BMI.[61] Fat mass and lean mass may need to be considered separately when analysing cardiac growth in

children, but most studies only had measures of BMI and we were thus unable to consider this.[62, 63]

We also found a lack of studies dealing with the longitudinal effects of RFs on cardiac function, and the few that did, investigated different aspects of systolic or diastolic function. Many of the populations included in the review have been young adults, and as such, the vast majority of study participants had normal cardiac function. As a result, it is not possible to make a generalised systematic assessment of the findings and this area would benefit from further research. Some findings have also been different among blacks and whites in the bi-ethnic studies. Further research with more heterogeneous study populations would be helpful in making findings more generalizable.

New research on the long-term effect of exposure to poorly controlled BP, BMI and glycaemia is warranted to better understand the mechanisms by which they independently, cumulatively or interactively affect later cardiac function and structure. The life course approach could help identify periods where exposures to RFs may be particularly detrimental to cardiac function and structure. This new knowledge would be invaluable to inform policy related to cardiovascular disease prevention, enabling earlier targeted intervention to individuals at risk.

Conclusions

This systematic review provides some evidence that earlier elevated BP, high BMI and poor glycaemic control result in worse cardiac structure and function up to 70 years later. This information may be used to inform clinical practice with the caveats that the number of studies on which this evidence is based is limited, and the findings are difficult to generalize to all population groups. There is a lack of studies investigating either the effect of changes in RFs over the life course or the cumulative effect of exposure to RFs on cardiac structure and function. Future studies utilizing a life course approach, to identify if there are sensitive periods where exposure is particularly detrimental, might suggest time-points when prevention may be most beneficial. Ultimately such information would be invaluable from a public health and preventive Cardiology perspective.

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Chapter 3

Methods

Data collection

Study patients

The UK Medical Research Council National Survey of Health and Development is a prospective birth cohort study of singleton births that occurred in one week of March 1946 in England, Scotland, and Wales (5362 births; 2547 women, 2815 men). Follow-up has included over 20 contacts with the whole cohort between birth and the most recent data collection when the participants were between 60-64y of age. At the most recent round of data collection, 3163 (59%) were included in the target sample; of the original cohort, 718 (13.4%) had died, 594 (11.1%) had previously withdrawn from the study, 567 (10.6%) lived abroad, and 320 (5.9%) had been permanently untraced for more than ten years.

Study members received postal questionnaires between 2007 and 2008 and were invited for clinic visits between October 2007 and February 2011. If study members were unable or unwilling to come to one of the six clinical research facilities located around the UK, they were offered a slightly less comprehensive examination (which did not include echocardiography),

carried out in their own home by a trained nurse. Of the 3163 people in the target sample, information was obtained from the postal questionnaire and/or visits from 2661 (84%). Of these, 1690 attended a clinic and 539 had a home visit.

Survey members had previously been interviewed in their own homes by trained research nurses at ages 36, 43 and 53y. The cohort profile has been described in detail previously.[1 2]

Blood pressure measurement

Brachial blood pressure (BP) was measured in the upper right arm with an appropriately sized cuff by a trained research nurse after 5 minutes of rest using an Omron HEM-705 machine (Omron Corporation, Tokyo, Japan).[3] The measurement was repeated twice with the second measurement used for analysis, or the first if the second was unavailable. This was done for consistency with previous visits. An Omron HEM-705 was also used when study members were aged 53y, while a Hawksley random zero sphygmomanometer (Hawksley & Sons Ltd, Lancin, UK) was used at ages 36 and 43y. BP values obtained with the random zero sphygmomanometer were corrected to enable comparison with BP measured with the Omron machine using an algorithm described by Stang et al.[4]

Antihypertensive medication (HTT)

HTT was recorded on the postal and clinic questionnaires at the most recent data collection. In previous years, study members had been asked about medications at the home visits. Drugs acting on the cardiovascular system for the last 2 rounds of data collection were classified

according to International Classification of Diseases and related Health Problems classification (ICD).[1, 2]

Anthropometric measurements

Height and weight were measured at 36, 43, 53 and 60-64y and self-reported at 20y (questionnaire) and 26y (home visit by interviewer).

In the last round of data collection, standing height in centimetres (to the nearest millimetre) was measured using a portable stadiometer with the head in the Frankfort plane. Weight at 60-64y was measured in Kg (to the nearest 0.1Kg) using Tanita solar weighting scales calibrated by Chasmors Limited (London, UK).

Standing height and weight were measured using the same equipment at ages 36-53y by research nurses during home visits. At 36y weight was recorded to the nearest 0.5Kg below and standing height to the nearest 0.5cm below. At 43y weight was recorded to the nearest 0.5Kg below and standing height to the nearest 1mm below. At 53y weight to the nearest 0.5Kg and standing height to the nearest 0.5cm were recorded. Imperial measurements at ages 20y and 26y were converted to metric values.

Body mass index (BMI), defined as weight (Kg) / height $(m)^2$ was calculated at each age. Those with a BMI of >= 25 Kg/m^2 were classed as overweight following the World Health Organization definition.[5]

We constructed an "age at first overweight" variable, which was the first age study members were recorded as overweight, provided they were recorded as overweight at all subsequent visits (Table 3.1). We were unable to define "duration of overweight" due to there being intervals between measurements, as overweight individuals may have been of normal weight

between clinic measures. Cohort members who were not persistently overweight (including those with missing data) were excluded from these analyses.

Table 3.1. Depiction of how age at first overweight was defined.

Age of first overweight (years)	Ages when documented as being overweight (years)
N/A	Never
60-64	60-64
53	60-64 + 53
43	60-64 + 53 + 43
36	60-64 + 53 +43 +36
26	60-64 + 53 + 43 + 36 + 26
20	60-64 + 53 + 43 + 36 + 26 + 20

Waist circumference was also measured but these data were not available for use at the time of analysis.

Type 2 diabetes mellitus

Presence of type 2 diabetes mellitus (T2DM) was used as a confounding variable in analyses. 175 cohort members reported that a doctor had diagnosed them with T2DM. Study members who were diagnosed with T2DM on the basis of their clinic blood tests were also included.

Echocardiographic studies

Of the 1690 participants who attended a clinic, 1653 [798 men and 855 women, mean age 63.3y +/- 1.1y (1SD)] underwent echocardiography using GE Vivid I machines (General Electric, Fairfield, Connecticut, USA) and 1480 had analysable images (89%). Echocardiographic images were obtained from parasternal long axis and short axis, apical 5-chamber, 4-chamber, 3-chamber, 2-chamber and aortic views along with conventional and tissue Doppler in the 4-chamber view. Image analysis was carried out by AKG along with two experienced cardiac physiologists masked to patient identity using GE EchoPac software.

A manual of operations was in place before my involvement in the project. I reviewed it and made some changes under the guidance of my supervisors. This modified manual of operations was followed by echocardiographers for all scans. I also carried out some scanning when echocardiographers were unavailable.

Measures of cardiac structure

Wall thickness

Wall thickness measurements were made in accordance with the latest American Society of Echocardiography (ASE)/ European Association of Echocardiography (EAE) guidelines on chamber quantification.[6] 2-dimensional (2D) targeted M-mode guided measurements were taken. Linear dimensions were taken of the septal wall, LV cavity, and posterior wall along the LV minor axis, identified as the largest diameter perpendicular to the septum and posterior wall according to the model of a prolate ellipse of revolution. M-mode images can often be of insufficient quality and as such criteria were established in the Manual of Operations as to acceptable image quality for measurement:

1) a single dominant line
2) continuous lines at the point of measurement at least 5 mm in length
3) an interface with motion characteristics for the specific cardiac structure

If the M-mode images were of insufficient quality, 2-Dimensional measurements were taken.

Left ventricular mass

Left ventricular mass (LVM) in our study has been calculated using the ASE/EAE recommended formula for deriving LVM from linear measurements[6]:

$$\mathrm{LVM} = 0.8 \times \left[1.04 \times \left[(\mathrm{LVIDD} + \mathrm{LVPWTD} + \mathrm{IVSD})^3 - (\mathrm{LVIDD})^3\right]\right] + 0.6\ \mathrm{g}$$

where LVIDD = LV internal diameter in diastole, LVPWTD = LV posterior wall thickness in diastole and IVSD = interventricular septal thickness in diastole

While this formula produces results which have been well correlated with necropsy (r = 0.90, p <0.001),[7] it does model the left ventricle (LV) as a prolate ellipse of revolution. As such, this formula is valid only for those patients without significantly abnormal LV geometry and errors in measurement can be magnified as measurements are cubed.

LVM is usually indexed (LVMI) to facilitate comparison with others/sexes and the use of normal value charts. The best method of indexing LVM remains a topic of debate.[8, 9] Body surface area (BSA) has been the commonest parameter used for indexing in clinical trials[6] and this has method been used in this thesis with the Dubois formula being used to calculate BSA.[10] However, a problem with using BSA is that LV hypertrophy (LVH) will be underestimated in obese individuals. To account for this, allometric indexing has also been advocated (height$^{2.7}$).[11, 12] LVM was also indexed to height$^{2.7}$ in this work for some comparative analyses.

Relative wall thickness

Relative wall thickness (RWT) was also calculated to allow differentiation of LV remodelling patterns (Figure 3.1):

$$RWT = \frac{2\ X\ LVPWTD}{LVIDD}$$

where LVIDD = LV internal diameter in diastole and LVPWTD = LV posterior wall thickness in diastole

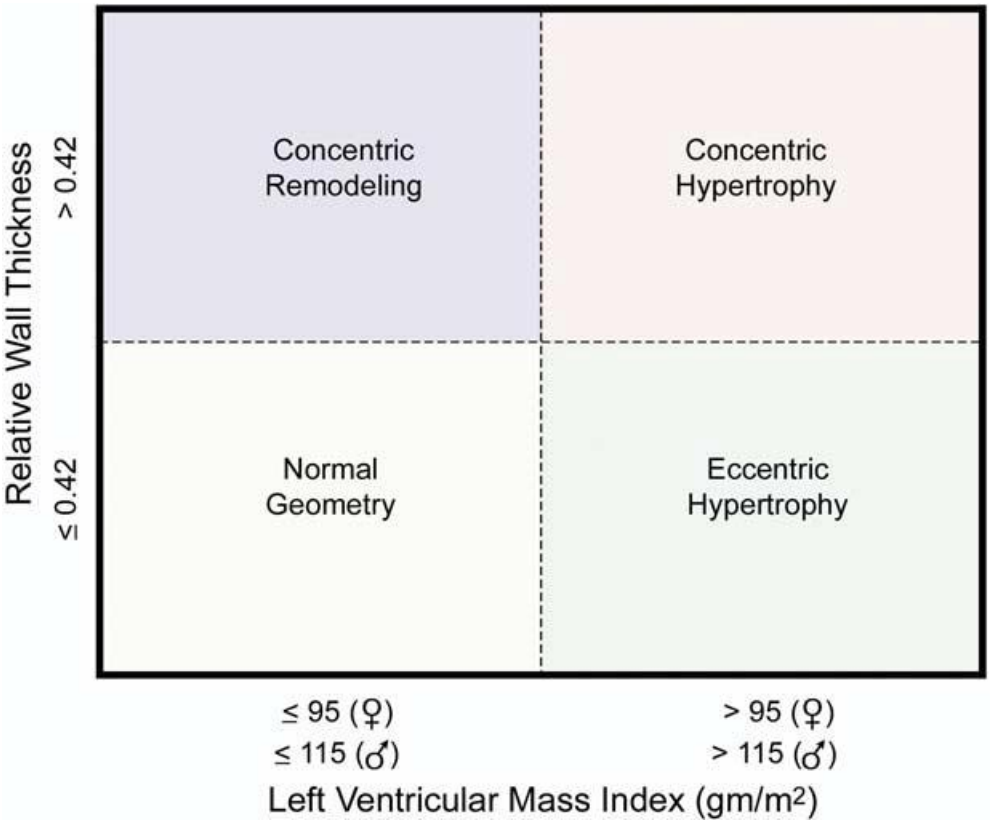


Figure 3.1. Comparison of relative wall thickness (RWT). Patients with normal left ventricular (LV) mass can have either concentric remodelling (normal LV mass with increased RWT >=0.42) or normal geometry (RWT <=0.42) and normal LV mass. Patients with increased LV mass can have either concentric (RWT >=0.42) or eccentric (RWT <=0.42) hypertrophy. These LV mass measurements are based on linear measurements.[6]

Measures of cardiac structure

Diastolic function

Pulsed wave Doppler in the 4 chamber view was used to acquire mitral inflow velocities which can help assess LV filling.[13] The flow pattern typically consists of two components – the E wave and A wave, associated with early filling and atrial contraction respectively (Figure 3.2).

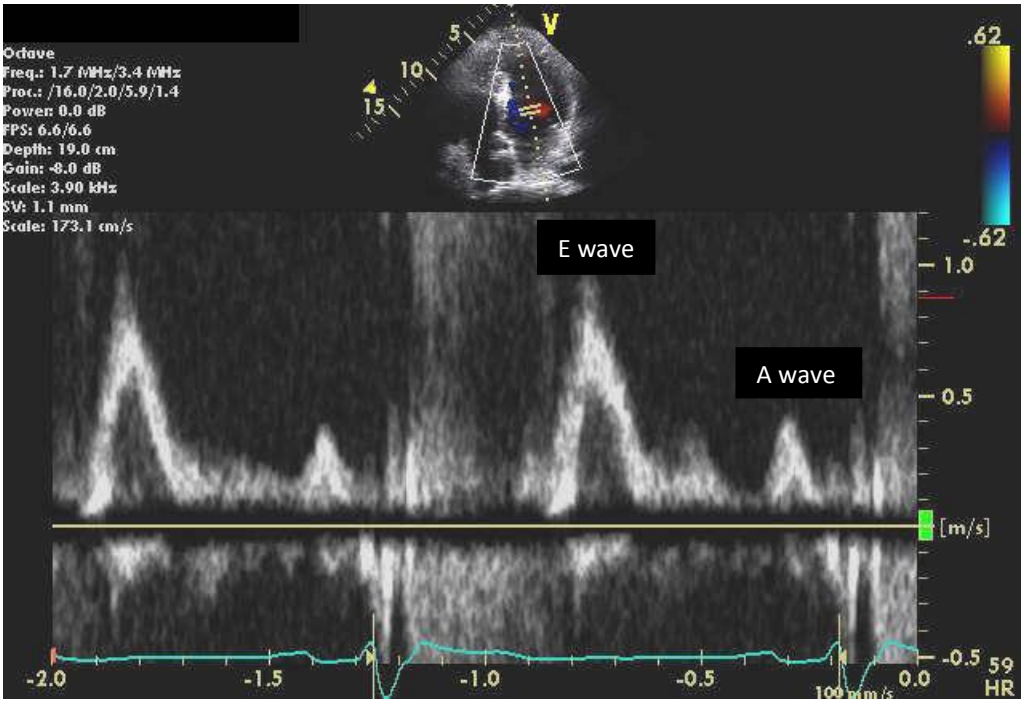
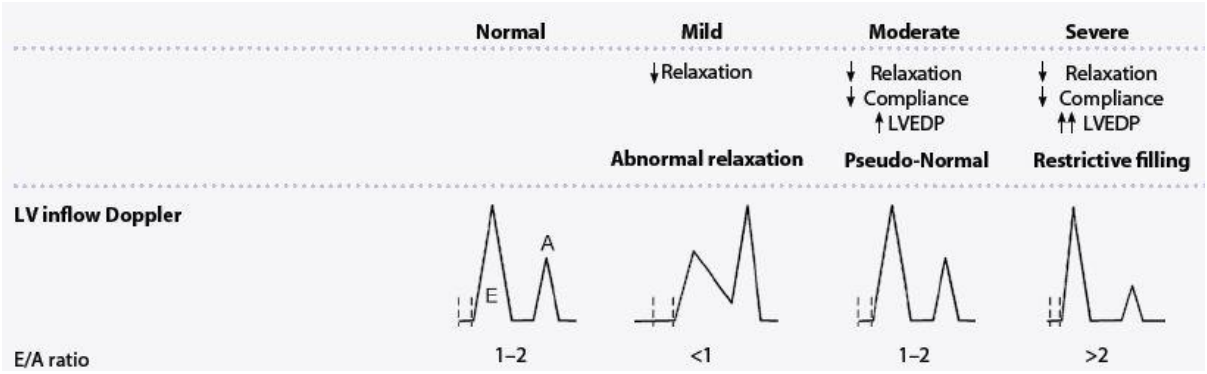


Figure 3.2. Normal mitral inflow pattern acquired by pulsed wave Doppler.[14]

The mitral E wave velocity primarily reflects the pressure gradient between the left atrium (LA) and LV in early diastole, which is largely established by relaxation of the left ventricle aspirating blood into itself.[15] The A wave results from a pressure gradient established by atrial contraction in late diastole. The ratio of the two (E/A) is a normalized index that reflects early

diastolic filling relative to atrial contraction[16] and has been widely used as an indicator of diastolic function.

The E and A waves can be influenced by a variety of factors. The E wave can be affected by preload and changes in LV relaxation, volumes, elastic recoil and diastolic pressures.[17] The A wave can be affected by LV compliance (the relationship between LV pressure and volume) and LA contractility.[18] Another limitation of E and A measurements is that LV filling patterns have a "U-shaped" relationship with diastolic function. Diastolic dysfunction is usually accompanied by a progressive increase in LV filling pressures. Slowed or prolonged LV relaxation causes a decrease in E velocity but at the same time contributes to elevation of LA pressure, which in turn tends to increase the E velocity.[19] This is usually accompanied by a decrease in compliance and, as a result, with time the effects of worsening diastolic function on E/A become progressively compensated and then over-compensated by the effects of loading and reduced compliance, resulting in an "U–shaped" non-linear relation between E/A and the severity of diastolic dysfunction.[20] Due to this, subjects with a E/A of 1-2 could have normal or abnormal diastolic function – the "pseudonormalization" phenomenon (Figure 3.3).[21]



LVEDP – Left ventricular end diastolic pressure.

Figure 3.3. Schematic diagram of the changes in mitral inflow in response to changes in the transmitral pressure gradient.[21]

To overcome this problem of pseudonormalization, other markers of diastolic function have to been developed. In this work, I have also utilized tissue Doppler to provide additional information on diastolic function. Pulsed wave tissue Doppler imaging in the 4-chamber view was used to obtain mitral annular velocities.[22] The velocities that are recorded are analogous to those obtained with pulsed wave Doppler – e' represents early diastolic annular velocity (analogous to E wave) and a' represents late diastolic annular velocity (analogous to the A wave) (Figure 3.4). e' progressively reduces as LV long axis relaxation is impaired and it is much less susceptible to the effects of increased preload.[18] Velocities at the lateral and septal annulus are not interchangeable[23] and the ASE/EAE[14] have recommend using the average of septal and lateral velocity; this was done in this thesis.

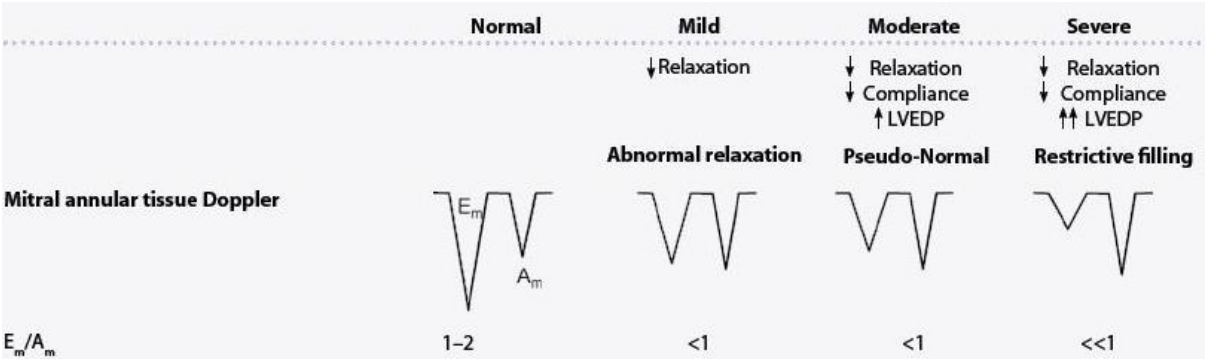


s' - systolic annular motion; e' and a' - respective early and late diastolic annular motion

Figure 3.4. Tissue Doppler recording from the lateral mitral annulus.

The ratio E/e' is used to provide an estimate of mean LA pressure. E/e' has been validated in a number of clinical situations[24] and is related to prognosis.[25-27] Currently, it is the favoured primary measure of diastolic function, as advocated by the latest (2009) joint EAE/ASE guidelines.[14, 28]

Another advantage of tissue Doppler, is that unlike pulsed wave Doppler across the mitral valve, there is no "U-shaped" relationship between the velocities and diastolic function and thus no pseudonormalization of e'/a' (Figure 3.5).



LVEDP – Left ventricular end diastolic pressure; E_m - e'; A_m - a'.

Figure 3.5. Schematic diagram of the changes in tissue Doppler mitral annular velocities in response to changes in the transmitral pressure gradient.[21]

Left atrial volume indexed to body surface area (LAVI) was also examined as a marker of chronic left ventricular filling pressures.[29, 30] Simpson's biplane method was used to calculate the volume of the left atrium.[6, 31] Simpson's algorithm uses the method of discs dividing the left atrium into a series of stacked oval discs (height =h, orthogonal minor axis = D_1, orthogonal major axis = D_2). The volume of the left atrium is then calculated as follows:

$$Left\ atrial\ volume = \frac{\pi}{4}\ X\ h\ \Sigma\ [(D_1)\ X\ (D_2)]$$

where h = left atrial height, D_1 = orthogonal minor axis, D_2 = orthogonal major axis

Systolic function

Systolic function has been measured in this thesis in the form of ejection fraction – EF and tissue Doppler velocity of systolic motion of the mitral annulus (average of the lateral and septal annulus) – s'.

EF is the fraction of blood ejected at each beat:

$$EF = \frac{LVEDV - LVESV}{LVEDV}$$

where LVEDV = left ventricular end diastolic volume and LVESV = left ventricular end systolic volume

Simpson's biplane method of discs was used to calculate the EF using two orthogonal views (2 chamber and 4 chamber). Using Simpson's biplane method can sometimes be problematic due to poor endocardial border definition.[6] In these situations, linear methods (2-D guided M mode) were used. However, a difficulty with using linear measures is that regional wall abnormalities may not be reflected in the EF value, or conversely, they may lead to a reduced EF not in keeping with global LV function which may be within normal limits.

While EF does correlate well with prognosis in heart failure of any aetiology,[32-35] s' may be a more sensitive marker of systolic dysfunction and is often depressed before there is any change in ejection fraction[36] and can detect subclinical systolic dysfunction in diabetic patients[37] and in patients with pre-clinical genetically-proven hypertrophic cardiomyopathy.[38] s' is also a predictor of cardiovascular events and mortality.[39-42]

Other measures of systolic function include endocardial fractional shortening, midwall fractional shortening, stress-corrected midwall fractional shortening and active fibre stress. These measures were not calculated in this thesis.

Quality control for echocardiographers

Standardized training for echocardiographers had taken place before data collection had started (before I was recruited as a PhD student). I arranged training for new echocardiographers who were assigned to the data collection team as well as arranging refresher training sessions.

All scans were reviewed by either myself or a member of the data collection team trained in image-quality interpretation and the manual of operations. Regular monthly feedback was provided to the echocardiographers and more frequent feedback was given if necessary. Retraining was planned if problems persisted, but in practice this did not prove necessary. If there were any significant clinical abnormalities, the participant was referred for a full echocardiogram, which was carried out and reported locally by an experienced Cardiologist.

I also carried out calibration testing of the Vivid GE machines at all the 6 clinical research facilities using a CIRS ultrasound phantom 055A (CIRS Incorporated, Norfolk, VA, USA). The images from the calibration testing of the 2D probe at one of the clinical research facilities is given below (Figure 3.6).

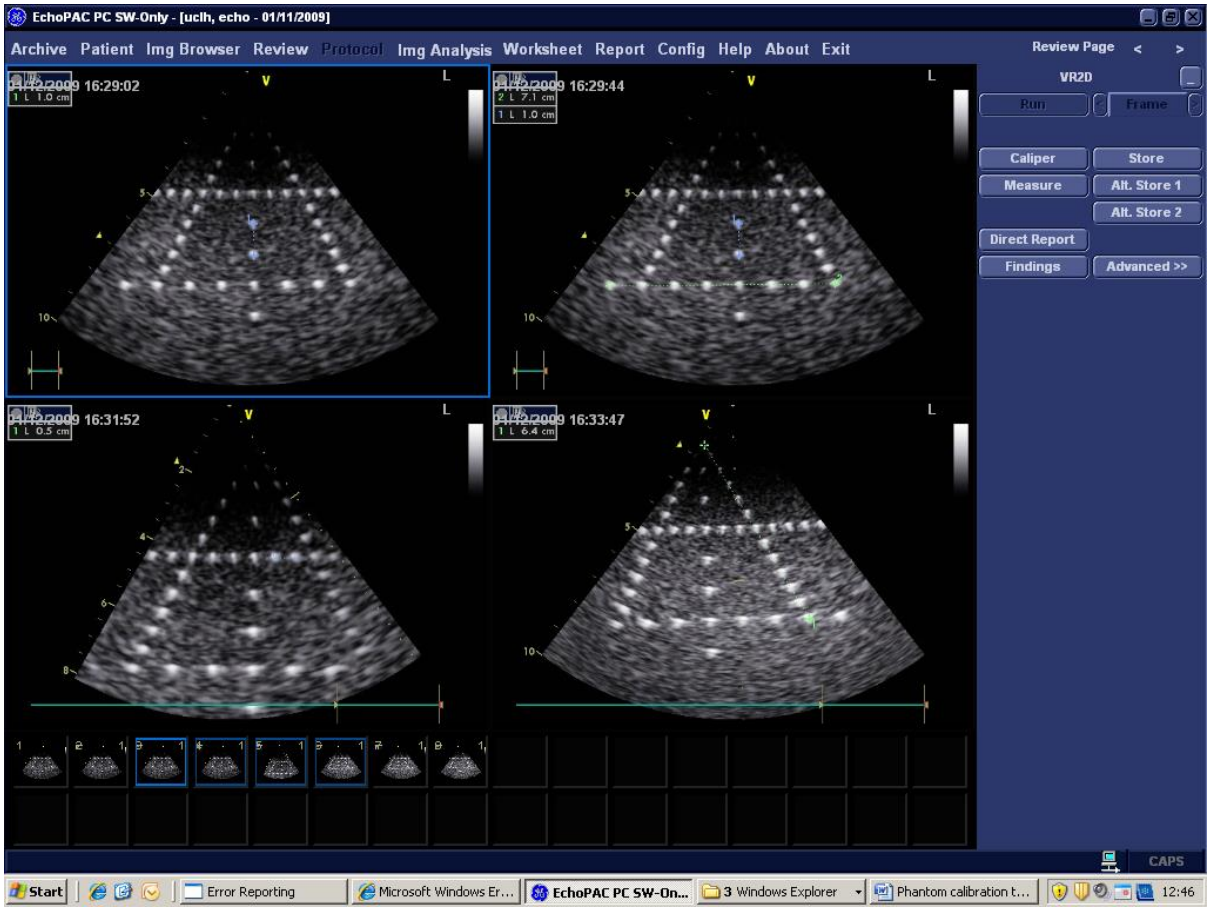


Figure 3.6. Screenshot of phantom calibration testing of 2D ultrasound probe.

Quality control for readers

Scans were read by me and 2 experienced echocardiographers. I had input into the preparation of a standardised image-reading protocol which was used to analyse the images offline using GE EchoPac software. A pre-specified analysis protocol was created in EchoPac by a GE technician under my guidance to streamline the reporting process.

Blind duplicate reading reproducibility studies were carried out to establish inter- and intra-reader variability with excellent reproducibility [intra-class correlation coefficients (ICCs)

were >90% for most measurements]. The results for some of the measures analysed in this thesis are documented in table 3.2.

Table 3.2. Intra-reader and inter-reader ICCs for Interventricular septal thickness in diastole, left ventricular internal diameter in diastole, e' and E/A.

Variable	Intra-reader ICC (reader 1)	Intra-reader ICC (reader 2)	Intra-reader ICC (reader 3)	Inter-reader ICC
IVSD	0.916	0.922	0.916	0.932
LVIDD	0.968	0.969	0.968	0.968
e'	0.907	0.911	0.906	0.919
E/A	0.979	0.979	0.980	0.981

ICC -Intra-class correlation coefficient; IVSD - Interventricular septal thickness in diastole; LVIDD - Left ventricular internal diameter in diastole

Bland-Altman plots were also constructed for the reproducibility exercise. The Bland-Altman plots for left ventricular internal diameter in diastole (LVIDD) measured by the 3 readers are given below (Tables 3.3a-c and Figures 3.7a-c).

Reader 1 vs. Reader 2

Table 3a. Mean, standard deviation, limits of agreement, p for bias and random error for left ventricular internal diameter in diastole (cm) measured by reader 1 (AG) and reader 2 (AO).

Measurement	Results
Mean ± SD (cm)	Reader 1 4.62 ± 0.68 vs. Reader 2 4.72 ± 0.79
Difference ± SD (cm)	-0.00 ± 0.25
Limits of agreement	-0.55, 0.54
p for bias	0.97
± random error	0.54

SD - Standard deviation

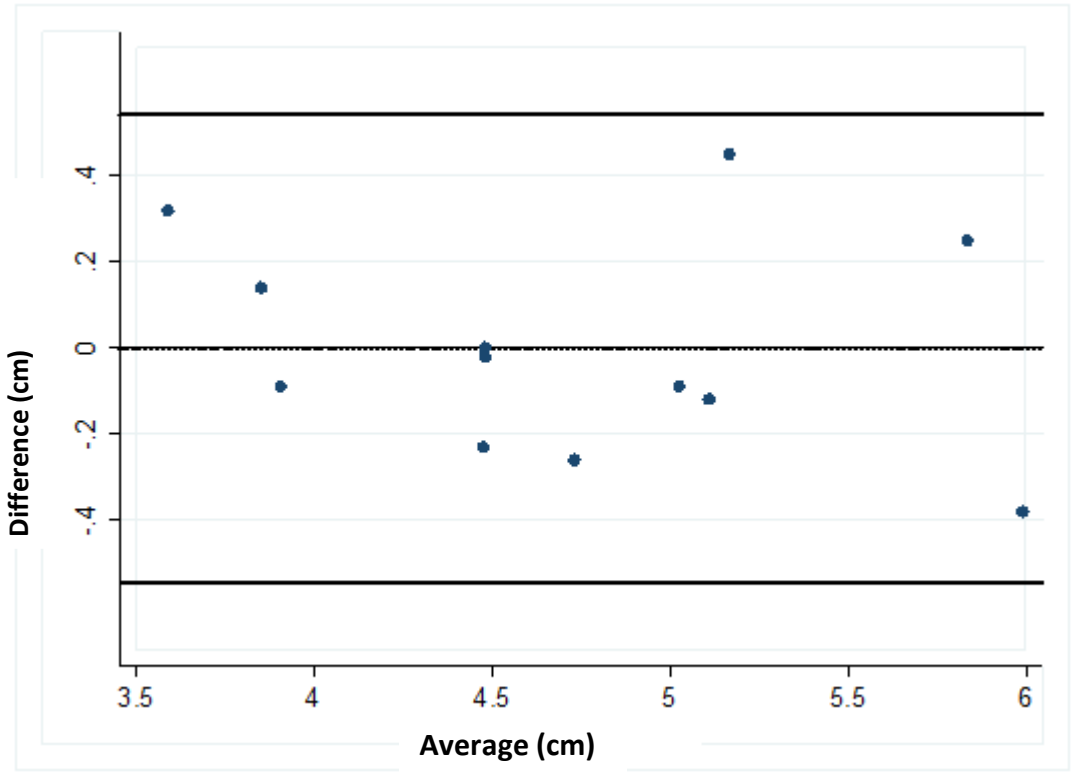


Figure 3.7a. Bland-Altman plot for left ventricular internal diameter in diastole (cm) measured by reader 1 (AG) and reader 2 (AO).

Reader 1 vs. Reader 3

Table 3.3b. Mean, standard deviation, limits of agreement, p for bias and random error for left ventricular diameter in diastole (cm) measured by reader 1 (AG) and reader 3 (KM).

Measurement	Results
Mean ± SD (cm)	Reader 1 4.62 ± 0.68 vs. Reader 3 4.68 ± 0.67
Difference ± SD (cm)	-0.03 ± 0.13
Limits of agreement	-0.30, 0.24
p for bias	0.34
± random error	0.27

SD - Standard deviation

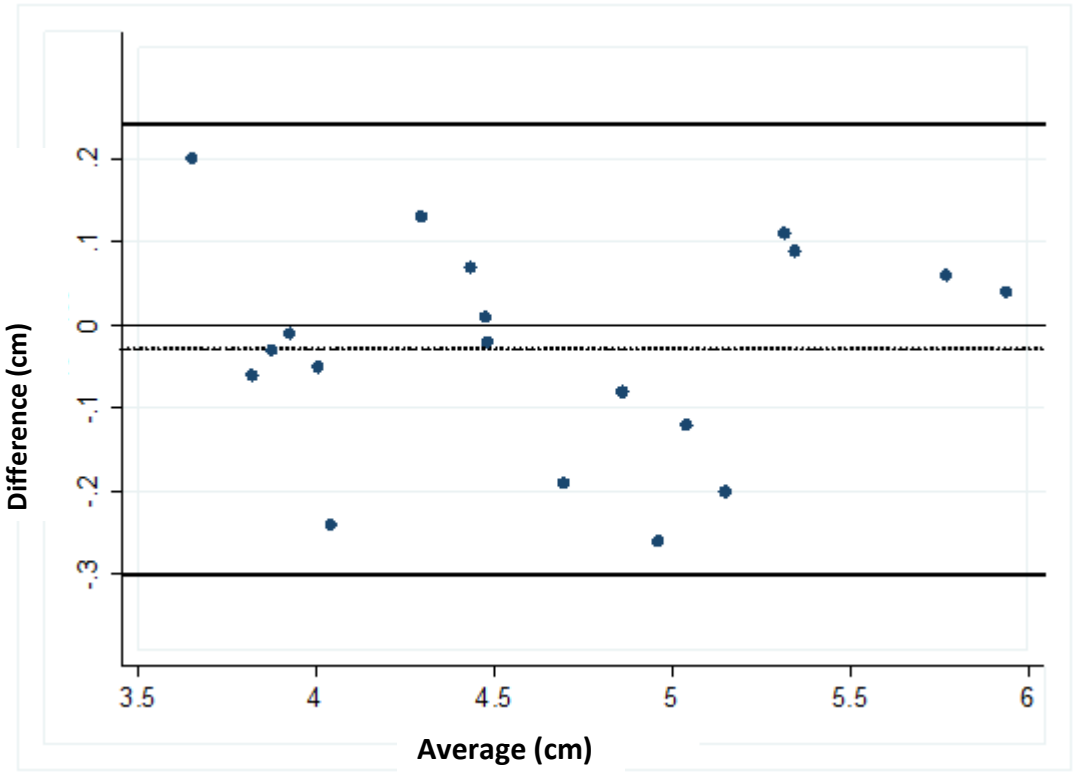


Figure 3.7b. Bland-Altman plot for left ventricular internal diameter in diastole (cm) measured by reader 1 (AG) and reader 3 (KM).

Reader 2 vs. Reader 3

Table 3.3c. Mean, standard deviation, limits of agreement, p for bias and random error for left ventricular internal diameter in diastole (cm) measured by reader 2 (AO) and reader 3 (KM).

Measurement	Results
Mean ± SD (cm)	Reader 2 4.72 ± 0.79 vs. Reader 3 4.68 ± 0.67
Difference ± SD (cm)	-0.00 ± 0.22
Limits of agreement	-0.49, 0.49
p for bias	0.99
± random error	0.49

SD - Standard deviation

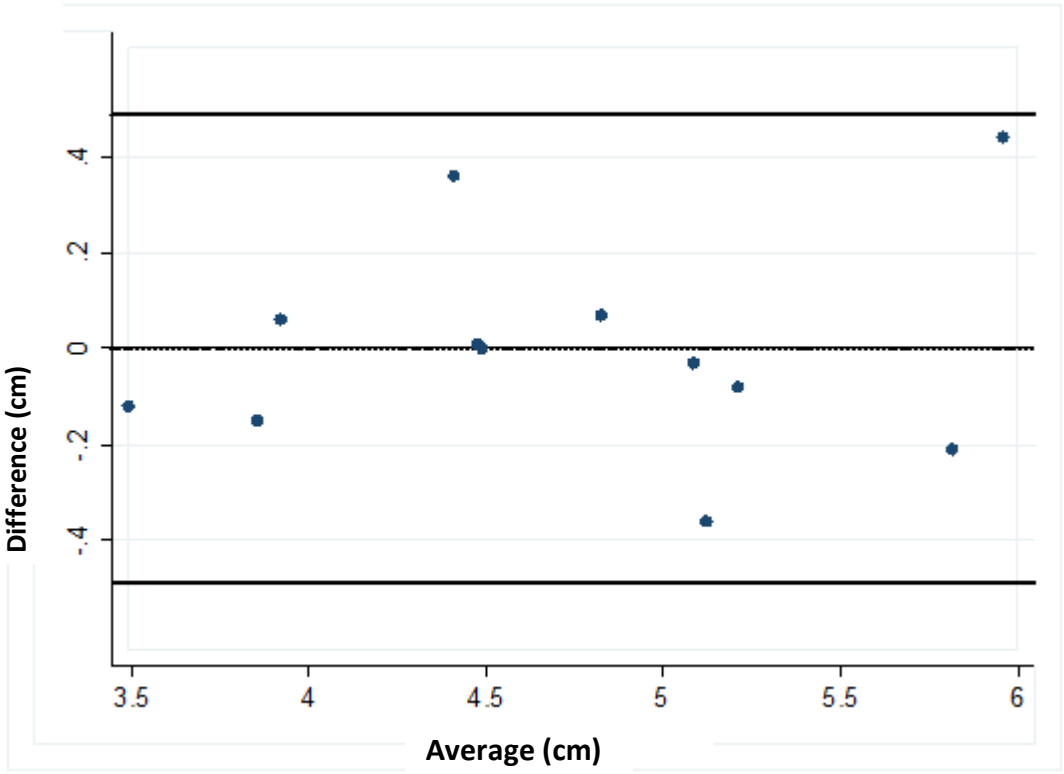


Figure 3.7c. Bland-Altman plot for left ventricular internal diameter in diastole (cm) measured by reader 2 (AO) and reader 3 (KM).

Coding the data

Codes were created for the various possible reasons why a study member did not undergo echocardiography and for the reasons for poor image quality. I was involved in coding the questionnaires using the above codes.

Data cleaning

All the echocardiographic measures and BP and heart rate readings were checked and cleaned prior to analysis (including those echocardiographic measures which were not used for analyses in this thesis). Means and 2 standard deviations were tabulated our measurements compared to the published data.[6, 14, 28, 31, 43] Outliers (outside 2 standard deviations) were individually inspected. This inspection involved reviewing measurements documented in the clinic questionnaire (e.g. BP and heart rate) or reviewing echocardiographic images themselves and re-measuring. For some of the echocardiographic measures, other related measurements were also checked (e.g. left atrial volume was checked if left atrial diameter was outside the 2 standard deviation range).

Normality of the data was checked by visually inspecting the distributions of the measurements once they had been cleaned. As the measurements used in this thesis were normally distributed no transformations (e.g. logarithmic) were performed. Once cleaned, the

variables were renamed with a suffix to indicate that they were the final variables to be used in analyses.

Statistical modelling

In the context of this thesis I have attempted to relate longitudinal changes in risk factors to future echocardiographic outcomes. While the converse approach has been applied in the literature (e.g. relating longitudinal changes in repeated echocardiographic measures to a single risk factor measurement i.e. changes in left ventricular mass over time in hypertensive patients in the Framingham cohort papers),[44, 45] there are no birth cohorts that have been analysed in the same manner as in this thesis.

With the repeated measures of risk factors in adult life I have aimed to determine if changes in these risk factors over time exert an influence on later cardiac structure and function and whether exposure to these risk factors at particular time points is more detrimental than at other times (sensitive period hypothesis). The rationale of this approach in a clinical context has also been discussed in the introduction of chapter 2.

Descriptive analysis

Data are presented as means with 95% confidence intervals. Data cleaning and checking for normality has been described above.

Initial BP and BMI analyses and adjustment for potential confounders

Initial analyses were carried out using linear regression with the cardiac variable as the outcome measure. Similar analyses were carried out for BP and BMI using comparable models and adjustments were made for similar confounders. The BP analyses are described initially followed by the BMI analyses.

Initial BP analyses

The predictive power of BP at different ages on subsequent cardiac structure and function was tested. Adjustments were initially made for the basic potential confounders age, sex and clinic attended. Given that the participants were aged between 60-64y when they underwent echocardiography, age was adjusted for. Six national clinics were used in this study and this could have led to geographical variations in the echocardiographic measures, so this was also accounted for.

Since some BP measurements were made while participants were on HTT, we assessed the impact of treatment on cardiac structure and function. We therefore added HTT at the respective age of BP measurement to the models. BP at age 60-64y was then included in the

model to determine if previous BP had an independent association with the cardiac outcome. This was done to determine if the association could be fully explained by tracking (or not).

T2DM and BMI being potential confounding variables were then included in the model.

The regression analysis relating the association of BP at age 36y on cardiac structure at age 60-64y is diagrammatically represented in Figure 3.8.

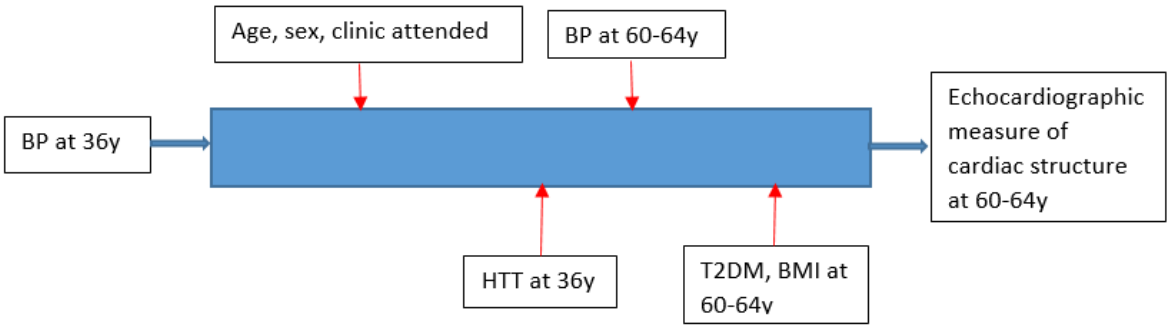


Figure 3.8. Diagrammatic representation of regression analysis of the effect of BP at 36y on cardiac structure at 60-64y (as measured by echocardiography) with successive adjustments (BP – blood pressure, HTT – hypertension treatment, T2DM – type 2 diabetes mellitus, BMI – body mass index)

For the models investigating cardiac function, LVMI was included in the final adjustment to determine if the associations were independent of cardiac dysfunction caused by BP-related changes in LVMI.

Residuals were also calculated, graphically plotted and reviewed for the models.

Initial BMI analyses

For the BMI analyses, the effect of BMI and overweight at the different ages on measures of cardiac function was examined using linear regression models similar to those used for the corresponding BP analyses.

Initial adjustments were made for age, sex and clinic attended. Subsequent adjustments were made for the potential confounders systolic BP (SBP) and T2DM at age 60-64y. The final model included BMI at age 60-64y (or overweight at age 60-64y for the overweight models) to determine if previous BMI (or overweight) was predictive of cardiac structure independent of BMI (or overweight) at 60-64y. For the BMI-cardiac function analyses, adjustment for LVMI (for the same rationale as in the BP-cardiac function models) was made prior to final adjustment with BMI or overweight at age 60-64y.

Multinomial regression analysis was performed when non-ordered categorical variables were included in the regression models. This was done for analyses involving LVH and RWT.

Further SBP analyses

The Accumulation Approach for SBP

The accumulation hypothesis has been previously tested by relating area-under-the-curve (AUC) of BP or BMI change to cardiac outcomes.[46] We initially investigated the utility of the AUC approach to test the cumulative effect of SBP on future cardiac structure by fitting linear regression models including the slope and intercept as predictor variables with an echocardiographic variable as the outcome measure. To construct the AUC model, we used a slope and intercept previously derived by a colleague which covered SBP change from 36y to 53y.[47] Initially, a multilevel model was constructed for each component of SBP, from which individual fitted random intercepts (which represent BP at 36y) were extracted along with slopes (which represent changes in BP from 36-53y).[47] The AUC was then derived by calculating the area covered by the rectangle (A) and triangle (B) obtained by plotting the rate of change in SBP from 36-53y (Figure 3.9). We then included SBP at age 60-64y in the model to determine if the effect of AUC from 36-53y was independent of SBP at age 60-64y. Analyses indicated that it was the slope, i.e. the rate of change, that largely determined the AUC because the majority of participants exhibited increasing BP over the period 36-53y. The association between AUC and cardiac outcome was thus driven by the effect of rate of change. As such, we decided to examine the rate of change in BP from 36-60/64y to determine if there was a sensitive period for BP change (described below).

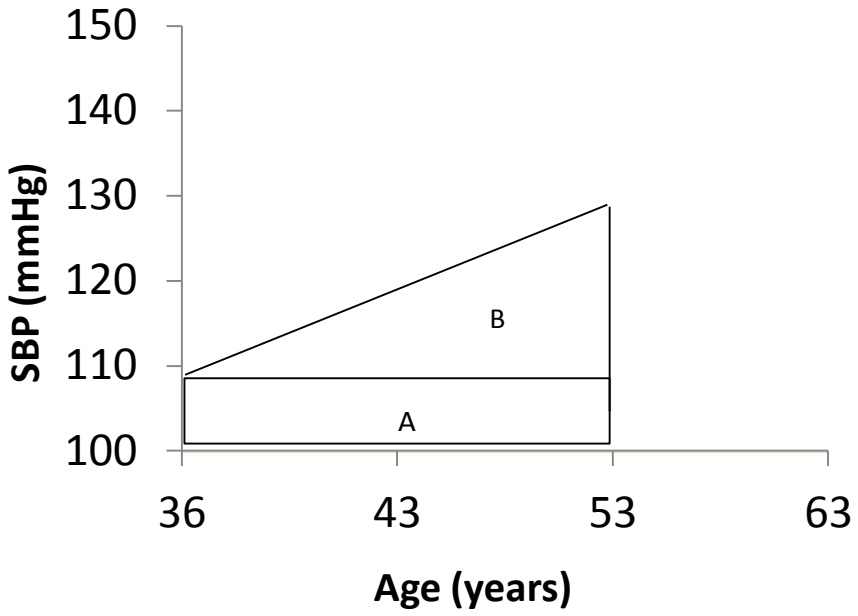


Figure 3.9. The components of the Area under a Curve plot – A and B (see text for details).

The Sensitive Period Approach for SBP

We decided to look at the effect of rate of change in BP on future cardiac structure and function to determine if there was a sensitive period among them. To test for a sensitive period, the study duration had to be divided into periods. BP had been measured 4 times in our cohort, so this allowed division into 3 periods: 36-43y, 43-53y and 53-60/64y. The change in SBP for the periods 36-43y, 43-53y and 53-60 to 64y *conditional* on earlier SBP was calculated. This was done by linear regression of each BP measure (from age 43y onwards) on the earlier measure(s) for each sex and saving the residuals i.e. for the first regression the

time period 36-43y was used, while for the second regression the time period 53-43y was used, taking into account what had gone before (BP at 36y) and so forth (Figure 3.10).

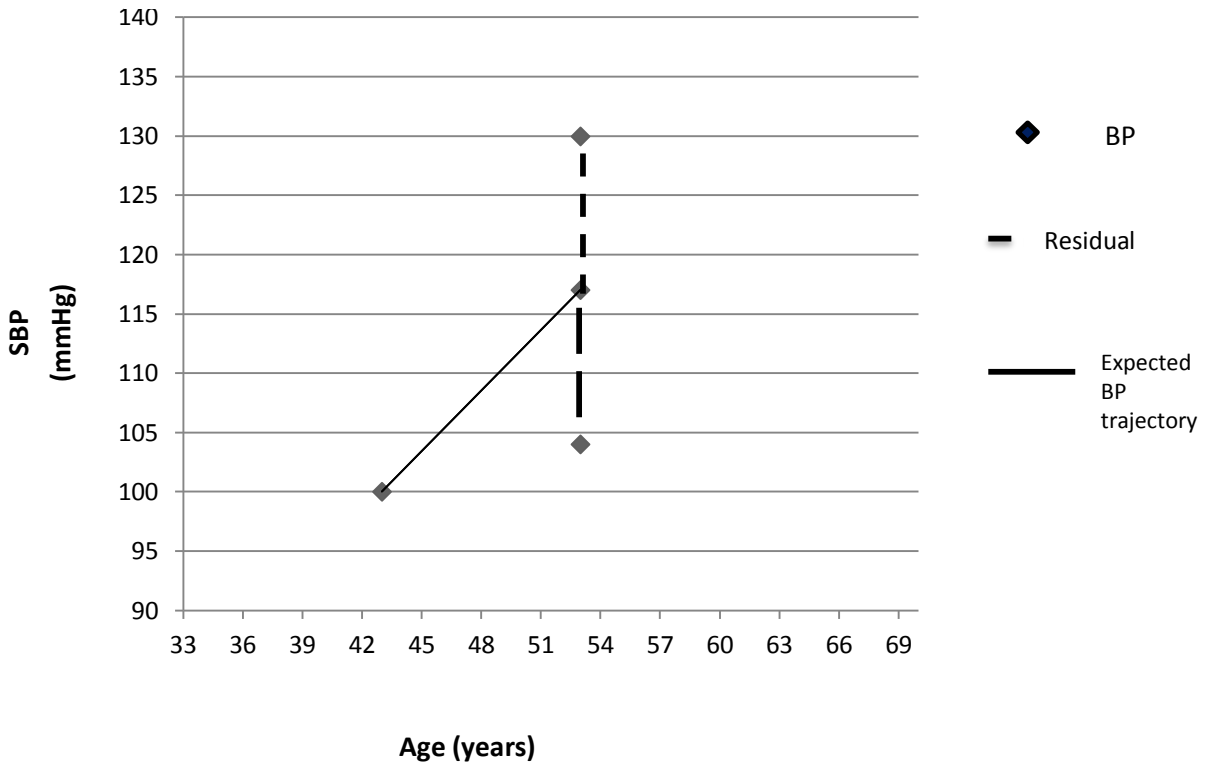


Figure 3.10. Graph illustrating expected BP trajectory over time along with BP of two individuals not on the expected trajectory (one above and one below). The residuals are also plotted (difference between the observed value and the predicted value).

These residuals reflect BP velocity and can be interpreted as the change in BP above or below that expected given earlier BP.[48] The residuals were then standardised (mean = 0 and standard deviation = 1) to allow a comparison of the relative associations between periods. Regression models were subsequently fitted including all these standardised changes with the echocardiographic measure as the outcome. By deriving change in this way, the 3 variables (i.e. the rates of change over the 3 periods) could be entered into the regression model, as they were uncorrelated (since the derived variables were conditional on past BP levels). The coefficients for each period were compared against each other using the Wald test (an approximation of the likelihood ratio test estimating whether the coefficient from one period is equal to the coefficient from another period). These models were then adjusted for possible confounders with initial adjustment made for age, sex and clinic attended and further adjustment for BMI, T2DM and HTT at age 60-64y.

Further BMI analyses

The effect of age at first overweight on cardiac structure and function was examined using the age at first overweight variable described previously. The sequence of adjustments was the same as for the BMI/overweight-cardiac structure/function analyses. Tests for linear trend across categories of age at overweight were obtained to determine if earlier overweight was related to worse cardiac outcome. Tests for deviation from linear trend were also carried out by using a likelihood ratio test to assess whether a model including age at first overweight as a categorical variable provided a better model fit than a model with age at first overweight fitted as a continuous variable (linear trend). Estimated marginal means were also calculated for the minimally adjusted models.

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Chapter 4

Effect of mid-life blood pressure change and treatment on subsequent left ventricular structure

Introduction

Blood pressure (BP) is a key risk factor for cardiovascular disease (CVD).[1, 2] Higher BP is also associated with increased left ventricular mass (LVM)[3] and left ventricular hypertrophy (LVH)[4] which are themselves related to subsequent CVD independent of current BP[3, 5] and increased LVM/LVH is a commonly used measure of hypertension-associated target organ damage.[6, 7]

Some studies have suggested that exposure to elevated BP or hypertension from early life onwards contributes to increased atherosclerosis and CVD in later life.[8-11] Currently, it is unclear whether this reflects tracking of BP across the life course, the cumulative burden of lifetime exposure to high BP, or the effect of high BP in a sensitive period. The long-term influence of hypertension therapy (HTT) has also been little explored, although in the short-term HTT causes regression of LVM and LVH and reduces CVD.[12, 13]

We therefore examined the effect of longitudinal changes in BP over the 28y period (ages 36y to 60-64y) on left ventricular (LV) structure as an indicator of target organ damage at 60-64y in the MRC NSHD. We also investigated the impact of HTT on BP-related changes in LV structure to explore the possible reversibility of the structural consequences of high BP.

Methods

The methods have been described in detail in the methods chapter (chapter 3).

Echocardiographic studies

Wall and LV chamber measures were made according to ASE/EAE guidelines.[14] LVM was indexed to body surface area (LVMI) as described in the methods chapter (chapter 3).

Statistical Analysis

This has been described in detail in the methods chapter (chapter 3).

Initially, separate regression models investigated the association between systolic BP (SBP) at each of the 4 ages at which it was measured and LVMI at 60-64y, with adjustment for sex, age at clinic visit and clinic attended. We tested whether these associations were linear and whether they were different for men and women. There was no evidence of a difference in association between men and women so in subsequent analyses both genders were pooled and adjusted for sex. HTT at the same age as BP measurement was then added to models. Additional models assessed whether earlier SBP remained predictive once current SBP was

also included. Final adjustments were made by including other possible confounders - BMI and T2DM at 60-64y. For the cross-sectional SBP model, we assessed whether any effect of HTT could be explained by prior BP.

To investigate whether rate of change in BP at a particular period of midlife was more strongly associated with LVMI, we used a rate of change in BP model described previously in the methods chapter (chapter 3).

The same analyses were repeated for diastolic BP (DBP), pulse pressure (PP) and mean arterial pressure (MAP) and for each of the other outcome measures [Interventricular septal thickness in diastole (IVSD), left ventricular posterior wall thickness in diastole (LVPWTD) and relative wall thickness (RWT)]. Predictors of LVH were analysed using multiple logistic regression.

Sensitivity analyses were carried out to assess whether the associations with SBP remained unchanged if those on HTT or those who were hypertensive (SBP>=140 mmHg and/or DBP >= 90mmHg) were excluded.

Results

The characteristics of the study sample are shown in Table 4.1. Those with un-analysable echocardiograms had higher BMI (28.8; SD=4.8 vs. 27.5; SD=4.6, p <0.001) and heart rate (71.1; SD=13.0 vs. 68.5; SD=11.8, p = 0.0082) than those with analysable scans.

Compared to men, women were older, had lower SBP, DBP, fasting triglyceride levels, fasting blood glucose levels and higher heart rates, fasting total cholesterol levels and fasting HDL cholesterol levels. BMI and prevalence of T2DM were similar between the sexes.

Men had larger left ventricular internal diameter (measured in diastole – LVIDD), IVSD, LVPWTD, RWT, LVM and LVMI.

Table 4.1. Echocardiographic and cardiac risk factor characteristics of study participants (Maximum sample had at least 1 echocardiographic measure of interest recorded = 1480) (Fasting blood samples used for glucose and lipid measures). Unless otherwise stated data refer to age 60-64y.

Variable (At age 60-64y unless stated otherwise)	Combined		Men		Women	
	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)
Age at echo (y)	1480	63.3 (1.1)	701	63.2 (1.1)	779	63.3 (1.1)
IVSD (cm)	1480	1.1 (0.2)	701	1.1 (0.2)	779	1.0 (0.2)
LVPWTD (cm)	1480	1.0 (0.2)	701	1.0 (0.2)	779	0.9 (0.2)
RWT	1480	0.4 (0.1)	701	0.4 (0.1)	779	0.4 (0.1)
LVM(g)	1480	181.3 (59.3)	701	209.2 (60.3)	779	156.1 (45.6)
LVMI-BSA (g/m^2)	1480	95.7 (26.6)	701	104.1 (27.9)	779	88.1 (22.9)
LVMI-$ht^{2.7}$ ($g/m^{2.7}$)	1480	44.2 (13.2)	701	46.1 (13.7)	779	42.4 (12.6)
SBP (mm Hg)	1478	135.7 (17.9)	701	139.0 (17.7)	777	132.8 (17.7)
SBP in those on HTT (mm Hg)	315	137.5 (17.6)	160	139.2 (18.2)	155	135.8 (16.8)
SBP in those not on HTT (mm Hg)	1011	135.1 (18.0)	457	138.6 (17.4)	554	132.1 (18.0)
SBP at 53y (mm Hg)	1393	134.1 (19.1)	657	137.8 (18.9)	736	130.7 (18.7)
SBP at 43y (mm Hg)	1381	121.5 (14.5)	654	123.0 (14.3)	727	120.1 (14.6)
SBP at 36y (mm Hg)	1334	118.3 (14.0)	631	121.3 (14.2)	703	115.6 (13.4)

DBP (mm Hg)	1478	77.4 (9.7)	701	79.0 (9.8)	777	75.9 (9.3)
DBP at 53y (mm Hg)	1393	83.4 (11.9)	657	86.2 (11.9)	736	80.9 (11.3)
DBP at 43y (mm Hg)	1381	78.5 (11.3)	654	80.9 (11.2)	727	76.3 (10.9)
DBP at 36y (mm Hg)	1333	76.0 (11.7)	630	77.8 (11.7)	703	74.4 (11.4)
HTT	1332		620		712	
On medication	315 (24)		159 (26)		156 (22)	
Heart Rate (bpm)	1473	68.5 (11.8)	699	67.2 (12.5)	774	69.7 (11.0)
BMI (Kg/m^2)	1480	27.5 (4.6)	701	27.7 (4.0)	779	27.4 (5.1)
Total cholesterol (mmol/L)	1386	5.7 (1.2)	657	5.4 (1.1)	729	6.0 (1.2)
HDL cholesterol (mmol/L)	1386	1.6 (0.4)	657	1.4 (0.3)	729	1.8 (0.4)
Triglycerides¶ (mmol/L)	1386	1.1 (0.8)	657	1.2 (0.9)	729	1.0 (0.7)
Assessed for T2DM	1357		635		722	
T2DM present	73 (6)		37 (6)		36 (5)	
Glucose (mmol/L)	1407	5.8 (1.2)	667	6.0 (1.2)	740	5.6 (1.2)
Hb_{A1c}	1387	5.8 (0.7)	656	5.8 (0.7)	731	5.8 (0.6)

¶ Median and interquartile range

SD - Standard deviation; IVSD - Interventricular septal thickness in diastole; LVPWTD - Left ventricular posterior wall thickness in diastole; RWT - Relative wall thickness; LVM - Left ventricular mass; LVMI-BSA - Left ventricular mass indexed to body surface area; LVMI-$ht^{2.7}$ - Left ventricular mass indexed to height raised to the power 2.7; SBP - Systolic blood pressure; HTT - Hypertension therapy; DBP - Diastolic blood pressure; BMI - Body mass index; HDL - High density lipoprotein; T2DM - Type 2 diabetes mellitus; Hb_{A1c} - Haemoglobin $_{A1C}$

Higher SBP from 36y onwards was associated with higher LVMI at 60-64y in a minimally adjusted model (Table 4.2a). Associations remained unchanged after adjustment for HTT.

From the age of 43y onwards, individuals on HTT had a higher mean LVMI than those who were not on treatment after adjusting for SBP at 60-64y.

We assessed the predictive value of previous BP over and above BP at 60-64y; SBP at age 53y remained associated with LVMI, with only marginal attenuation, whereas associations with SBP at ages 36y and 43y were considerably weakened. A model with SBP at 53y and at 60-64y, or equivalently change in SBP between 53-60-64y, provided an improvement in fit over the model with only SBP at age 60-64y ($p<0.001$), thus indicating that change in SBP between 53y and 60-64y adds to the cross-sectional SBP association. Further adjustment for BMI and presence of T2DM at 60-64y slightly attenuated the associations of SBP and HTT with LVMI but the relationship between SBP at 53y and LVMI remained.

The associations were similar when SBP was substituted with DBP, PP or MAP (Tables 4.2b-d) and when LVMI was substituted with IVSD or LVPWTD (Tables 4.2e-f).

We investigated the possibility that the relationship between HTT at 60-64y and LVMI could be explained by high prior BP. Inclusion of SBP at 53y attenuated the effect of HTT on LVMI from 11.01 (95% CI: 7.86, 14.15) to 7.83 (95% CI: 4.36, 11.29), while additional inclusion of SBP at younger ages had negligible effects.

Table 4.2a. Regression coefficients (g/m^2), 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on left ventricular mass indexed to body surface area at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36 (n = 1205)	**SBP**	0.17 (0.05, 0.28)	0.004	0.17 (0.05, 0.28)	0.004	0.11 (-0.01, 0.22)	0.072	0.10 (-0.01, 0.22)	0.083
	HTT	-	-	*0.89 (-13.49, 15.27)*	*0.903*	*2.08 (-12.20, 16.37)*	*0.775*	*-1.01 (-14.99, 12.97)*	*0.887*
Age 43 (n = 1237)	**SBP**	0.16 (0.06, 0.26)	0.003	0.15 (0.04, 0.25)	0.005	0.07 (-0.04, 0.18)	0.190	0.07 (-0.03, 0.18)	0.183
	HTT	-	-	*15.93 (6.60, 25.27)*	*0.001*	*16.15 (6.88, 25.41)*	*0.001*	*11.91 (2.73, 21.09)*	*0.011*
Age 53 (n = 1260)	**SBP**	0.29 (0.22, 0.36)	<0.001	0.25 (0.18, 0.32)	<0.001	0.22 (0.14, 0.30)	<0.001	0.19 (0.11, 0.27)	<0.001
	HTT	-	-	*10.07 (5.91, 14.22)*	*<0.001*	*10.19 (6.04, 14.34)*	*<0.001*	*7.85 (3.67, 12.02)*	*<0.001*
Age 60-64 (n = 1319)	**SBP**	0.20 (0.13, 0.28)	<0.001	0.19 (0.10, 0.26)	<0.001	-	-	0.15 (0.08, 0.23)	<0.001
	HTT	-	-	*11.01 (7.86, 14.15)*	*<0.001*	-	-	*8.37 (5.15, 11.58)*	*<0.001*

HTT - Hypertension therapy; SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

Table 4.2b. Regression coefficients (g/m^2), 95% confidence intervals and p values estimating the effect of DBP and HTT at 4 time points on left ventricular mass indexed to body surface area at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + DBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36 (n = 1186)	**DBP**	0.22 (0.07, 0.37)	0.005	0.22 (0.07, 0.37)	0.005	0.18 (0.02, 0.34)	0.027	0.16 (0.01, 0.31)	0.041
	HTT	-	-	*0.36 (-14.06, 14.77)*	*0.961*	*0.90 (-13.50, 15.29)*	*0.903*	*-2.05 (-16.09, 12.00)*	*0.775*
Age 43 (n = 1237)	**DBP**	0.19 (0.03, 0.35)	0.018	0.16 (0.01, 0.32)	0.043	0.12 (-0.05, 0.28)	0.161	0.09 (-0.07, 0.25)	0.276
	HTT	-	-	*15.68 (6.30, 25.06)*	*0.001*	*15.75 (6.40, 25.11)*	*0.001*	*11.38 (2.14, 20.62)*	*0.016*
Age 53 (n = 1260)	**DBP**	0.39 (0.27, 0.51)	<0.001	0.33 (0.21, 0.45)	<0.001	0.31 (0.18, 0.43)	<0.001	0.24(0.12, 0.37)	<0.001
	HTT	-	-	*11.10 (6.94,15.25)*	*<0.001*	*11.15 (6.99, 15.31)*	*<0.001*	*8.52 (4.34, 12.70)*	*<0.001*
Age 60-64 (n **=** 1319)	**DBP**	0.23 (0.10, 0.38)	0.001	0.22 (0.08, 0.37)	0.002	-	-	0.20 (0.06, 0.34)	0.005
	HTT	-	-	*11.33 (8.17, 14.49)*	*<0.001*	-	-	*8.44(5.22, 11.66)*	*<0.001*

HTT - Hypertension therapy; DBP - Diastolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

Table 4.2c. Regression coefficients (g/m^2), 95% confidence intervals and p values estimating the effect of PP and HTT at 4 time points on left ventricular mass indexed to body surface area at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + PP at 60-64y)		Model 4 (model 3 + T2DM + BMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36 (n = 1204)	**PP**	0.08 (-0.07, 0.23)	0.294	0.08 (-0.07, 0.23)	0.294	0.04 (-0.11, 0.19)	0.591	0.04 (-0.10, 0.19)	0.559
	HTT	-	-	*2.14 (-12.27, 16.54)*	*0.771*	*2.82 (-11.48, 17.13)*	*0.699*	*-0.35 (-14.35, 13.65)*	*0.961*
Age 43 (n = 1237)	**PP**	0.13 (-0.01, 0.27)	0.064	0.14 (-0.002, 0.276)	0.055	0.06 (-0.09, 0.20)	0.432	0.07 (-0.07, 0.21)	0.310
	HTT	-	-	*16.81 (7.47, 26.14)*	*0.001*	*16.78 (7.50, 26.05)*	*<0.001*	*12.46 (3.27, 21.65)*	*0.008*
Age 53 (n = 1260)	**PP**	0.31 (0.20, 0.41)	<0.001	0.26 (0.16, 0.37)	<0.001	0.22 (0.11, 0.33)	<0.001	0.19 (0.08, 0.30)	<0.001
	HTT	-	-	*11.69 (7.55, 15.83)*	*<0.001*	*11.68 (7.55,15.81)*	*<0.001*	*8.92 (4.76, 13.08)*	*<0.001*
Age 60-64 (n = 1319)	**PP**	0.23 (0.13, 0.33)	<0.001	0.21 (0.11, 0.31)	<0.001	-	-	0.16 (0.06, 0.26)	0.001
	HTT	-	-	*11.09 (7.93, 14.24)*	*<0.001*	-	-	*8.40 (5.18, 11.62)*	*<0.001*

HTT - Hypertension therapy; PP - Pulse pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

Table 4.2d. Regression coefficients (g/m^2), 95% confidence intervals and p values estimating the effect of MAP and HTT at 4 time points on left ventricular mass indexed to body surface area at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + MAP at 60-64y)		Model 4 (model 3 + T2DM + BMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36 (n = 1204)	**MAP**	0.24 (0.09, 0.39)	0.002	0.24 (0.09, 0.39)	0.002	0.17 (0.01, 0.32)	0.035	0.16 (0.01, 0.31)	0.043
	HTT	-	-	*0.27 (-14.13, 14.67)*	*0.971*	*1.32 (-13.01, 15.66)*	*0.856*	*-1.67 (-15.69, 12.34)*	*0.815*
Age 43 (n = 1237)	**MAP**	0.22 (0.07, 0.36)	0.004	0.19 (0.05, 0.34)	0.010	0.11 (-0.04, 0.27)	0.147	0.10 (-0.05, 0.25)	0.206
	HTT	-	-	*15.57 (6.21, 24.93)*	*0.001*	*15.78 (6.47, 25.09)*	*0.001*	*11.51 (2.30, 20.72)*	*0.014*
Age 53 (n = 1260)	**MAP**	0.41 (0.30, 0.51)	<0.001	0.35 (0.25, 0.45)	<0.001	0.31 (0.20, 0.43)	<0.001	0.26 (0.14, 0.37)	<0.001
	HTT	-	-	*10.24 (6.08, 14.40)*	*<0.001*	*10.36 (6.20, 14.52)*	*<0.001*	*7.96 (3.78, 12.14)*	*<0.001*
Age 60-64 (n = 1319)	**MAP**	0.28 (0.16, 0.41)	<0.001	0.26 (0.15, 0.38)	<0.001	-	-	0.22 (0.11, 0.34)	<0.001
	HTT	-	-	*11.14 (7.99, 14.29)*	*<0.001*	-	-	*8.39 (5.18, 11.61)*	*<0.001*

HTT - Hypertension therapy; MAP – Mean arterial pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

Table 4.2e. Regression coefficients (cm), 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on interventricular thickness in diastole at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36 (n = 1207)	**SBP**	0.00060 (-0.0004, 0.0016)	0.218	0.00060 (-0.0004, 0.0016)	0.217	0.000049 (-0.0009, 0.0010)	0.921	0.000090 (-0.0009, 0.0010)	0.851
	HTT	-	-	*-0.0038 (-0.125, 0.117)*	*0.950*	*0.0074 (-0.113, 0.127)*	*0.904*	*-0.026 (-0.142, 0.091)*	*0.665*
Age 43 (n = 1239)	**SBP**	0.0011 (0.0002, 0.0020)	0.014	0.0010 (0.0002, 0.0019)	0.021	0.0004 (-0.0006, 0.0013)	0.432	0.0004 (-0.0005, 0.0013)	0.348
	HTT	-	-	*0.122 (0.043, 0.201)*	*0.002*	*0.124 (0.046, 0.202)*	0.002	*0.079 (0.003, 0.155)*	*0.042*
Age 53 (n = 1262)	**SBP**	0.0022 (0.0016, 0.0028)	<0.001	0.0020 (0.0014, 0.0026)	<0.001	0.0016 (0.0010, 0.0023)	<0.001	0.0013 (0.0007, 0.0020)	<0.001
	HTT	-	-	*0.055 (0.020, 0.090)*	*0.002*	*0.056 (0.021, 0.091)*	*0.002*	*0.033 (-0.002, 0.068)*	*0.064*
Age 60-64 (n = 1321)	**SBP**	0.0017 (0.0011, 0.0024)	<0.001	0.0016 (0.0010, 0.0022)	<0.001	-	-	0.0012 (0.0006, 0.0018)	<0.001
	HTT	-	-	*0.083 (0.056, 0.109)*	*<0.001*	-	-	*0.053 (0.026, 0.079)*	*<0.001*

HTT - Hypertension therapy; SBP – Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

Table 4.2f. Regression coefficients (cm), 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on left ventricular posterior wall thickness in diastole at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36 (n = 1205)	**SBP**	0.00092 (0.0002, 0.0016)	0.015	0.00093 (0.0002, 0.0017)	0.015	0.000049 (-0.0003, 0.0923)	0.208	0.00052 (-0.0002, 0.0012)	0.155
	HTT	-	-	*-0.0097 (-0.104, 0.084)*	*0.840*	*-0.0008 (-0.094, 0.092)*	*0.986*	*-0.033 (-0.121, 0.056)*	*0.471*
Age 43 (n = 1237)	**SBP**	0.0014 (0.0007, 0.0021)	<0.001	0.0013 (0.0006, 0.0020)	<0.001	0.00080 (0.0008, 0.0015)	0.029	0.00086 (0.0002, 0.0015)	0.014
	HTT	-	-	*0.097 (0.035, 0.158)*	*0.002*	*0.098 (0.037, 0.159)*	0.002	*0.057 (-0.002, 0.116)*	*0.056*
Age 53 (n = 1260)	**SBP**	0.0018 (0.0013, 0.0022)	<0.001	0.0016 (0.0011, 0.0020)	<0.001	0.0012 (0.0007, 0.0018)	<0.001	0.00093 (0.0004, 0.0014)	<0.001
	HTT	-	-	*0.051 (0.023, 0.079)*	*<0.001*	*0.052 (0.025, 0.080)*	*<0.001*	*0.031 (0.004, 0.058)*	*0.026*
Age 60-64 (n = 1319)	**SBP**	0.0015 (0.0010, 0.0020)	<0.001	0.0014 (0.0009, 0.0019)	<0.001	-	-	0.0010 (0.0005, 0.0014)	<0.001
	HTT	-	-	*0.059 (0.0396, 0.080)*	*<0.001*	-	-	*0.030 (0.009, 0.051)*	*0.004*

HTT - Hypertension therapy; SBP – Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

The relationships between SBP and RWT were similar to those between SBP and LVMI, demonstrating associations of midlife SBP with RWT independent of SBP at 60-64y, although the association with SBP at 36y was weaker (Table 4.2g).

SBP from 53y onwards was associated with LVH independent of SBP at 60-64y (OR = 1.22, 95% CI = 1.05, 1.42) for a 1 SD increase in SBP at 53y adjusted for age, sex, clinic, HTT, SBP at 60-64y, T2DM and BMI.

The associations between SBP and LVMI remained unchanged when those on HTT or those who were hypertensive (SBP>=140 mmHg and/or DBP >= 90mmHg) were excluded (Tables 4.2h-i).

Table 4.2g. Regression coefficients, 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on relative wall thickness at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36 (n = 1203)	**SBP**	0.00017 (-0.00021, 0.00056)	0.377	0.00018 (-0.00012, 0.00057)	0.361	0.000040 (-0.00036, 0.00044)	0.840	0.00050 (-0.00035, 0.00045)	0.807
	HTT	-	-	*-0.015 (-0.064, 0.034)*	*0.559*	*-0.012 (-0.061, 0.037)*	*0.637*	*-0.018 (-0.067, 0.031)*	*0.465*
Age 43 (n = 1235)	**SBP**	0.00067 (0.00031, 0.00103)	<0.001	0.00066 (0.00030, 0.00102)	<0.001	0.00052 (0.00014, 0.00090)	0.007	0.00054 (0.00016, 0.00092)	0.005
	HTT	-	-	*0.018 (-0.015, 0.051)*	*0.281*	*0.019 (-0.014, 0.052)*	*0.259*	*0.011 (-0.022, 0.044)*	*0.511*
Age 53 (n = 1259)	**SBP**	0.00057 (0.00032 0.00082)	<0.001	0.00053 (0.00027, 0.00079)	<0.001	0.00042 (0.00014, 0.00070)	0.003	0.00037 (0.00088, 0.00065)	0.010
	HTT	-	-	*0.010 (-0.004, 0.025)*	*0.171*	*0.011 (-0.004, 0.026)*	*0.155*	*0.008 (-0.007, 0.023)*	*0.321*
Age 60-64 (n = 1317)	**SBP**	0.00047 (0.00020, 0.00073)	0.001	0.00045 (0.00018, 0.00071)	0.001	-	-	0.00037 (0.00098, 0.00063)	0.008
	HTT	-	-	*0.015 (0.004, 0.026)*	*0.010*	-	-	*0.009 (-0.002, 0.021)*	*0.122*

HTT - Hypertension therapy; SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

Table 4.2h. Regression coefficients (g/m^2), 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on left ventricular mass indexed to body surface area at 60-64 years (excluding those who are hypertensive BP >=140/90mmHg).

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36 (n = 1044)	**SBP**	0.12 (-0.02, 0.26)	0.095	0.12 (-0.02, 0.26)	0.095	0.050 (-0.093, 0.193)	0.491	0.047 (-0.093, 0.188)	0.509
	HTT	-	-	*2.01 (-16.59, 20.61)*	*0.832*	*2.82 (-15.54, 21.21)*	*0.762*	*-2.48 (-20.62, 15.65)*	*0.788*
Age 43 (n = 1001)	**SBP**	0.11 (-0.05, 0.26)	0.173	0.09 (-0.06, 0.24)	0.224	-0.02 (-0.18, 0.13)	0.758	0.005 (-0.148, 0.157)	0.952
	HTT	-	-	*16.33 (5.32, 27.35)*	*0.004*	*16.18 (5.34, 27.02)*	*0.003*	*11.89 (1.06, 22.73)*	*0.032*
Age 53 (n = 760)	**SBP**	0.24 (0.10, 0.38)	0.001	0.23 (0.10, 0.37)	0.001	0.17 (0.02, 0.32)	0.027	0.14 (-0.003, 0.289)	0.055
	HTT	-	-	*11.85 (6.20, 17.50)*	*<0.001*	*11.49 (5.84, 17.13)*	*<0.001*	*9.77 (4.18, 15.35)*	*0.001*
Age 60-64 (n = 788)	**SBP**	0.21 (0.05, 0.37)	0.012	0.20 (0.04, 0.36)	0.017	-	-	0.14 (-0.02, 0.30)	0.082
	HTT	-	-	*12.58 (8.56, 16.60)*	*<0.001*	-	-	*8.54 (4.32, 12.75)*	*<0.001*

HTT - Hypertension therapy; SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

Table 4.2i. Regression coefficients (g/m^2), 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on left ventricular mass indexed to body surface area at 60-64 years (excluding those on HTT).

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36 (n = 1193)	**SBP**	0.16 (0.05, 0.28)	0.006	0.16 (0.05, 0.28)	0.006	0.10 (-0.02, 0.22)	0.089	0.10 (-0.02, 0.21)	0.100
	HTT	-	-	-	-	-	-	-	-
Age 43 (n = 1209)	**SBP**	0.14 (0.04, 0.25)	0.007	0.14 (0.04, 0.25)	0.007	0.07 (-0.04, 0.18)	0.234	0.07 (-0.04, 0.18)	0.233
	HTT	-	-	-	-	-	-	-	-
Age 53 (n = 1108)	**SBP**	0.25 (0.17, 0.33)	<0.001	0.25 (0.17, 0.33)	<0.001	0.22 (0.13, 0.30)	<0.001	0.19 (0.11, 0.27)	<0.001
	HTT	-	-	-	-	-	-	-	-
Age 60-64 (n = 1009)	**SBP**	0.21 (0.13, 0.29)	<0.001	0.21 (0.13, 0.29)	<0.001	-	-	0.14 (0.06, 0.22)	0.001
	HTT	-	-	-	-	-	-	-	-

HTT - Hypertension therapy; SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

Evidence for a sensitive period in midlife

Faster increases in SBP between 43-53y and 53-60/64y were significantly related to greater LVMI with or without adjustment for HTT, T2DM and BMI (Table 4.3), whereas increased rate of change in BP between 36-43y was only weakly related to LVMI. The relationship between rate of change in SBP between 43-53y was significantly stronger than the other two intervals ($p = 0.001$ for both) and this was essentially unaffected by adjustment for current risk factors.

Table 4.3. Regression coefficients (LVMI unit per unit SD change), 95% confidence intervals, and p values for a model showing effect of rate of change in SBP over 3 time periods (36-43y), (43-53y) and (53-60 to 64y) on LVMI at age 60-64y. Initial model adjusted for sex, age at clinic attendance and clinic attended. Final model also adjusted for BMI, T2DM and HTT.

Period of rate of change in SBP	**Adjusted for sex, clinic attended and age**		**Also adjusted for BMI, T2DM and current HTT**	
	β Coefficient (95%CI)	*p value*	*β Coefficient (95%CI)*	*p value*
36y – 43y	1.42 (-0.16, 3.00)	0.078	0.48 (-1.12, 2.08)	0.555
43y – 53y	5.20 (3.69,6.72)	<0.001	3.16 (1.59, 4.73)	<0.001
53y – 60/64y	1.53 (0.06, 3.01)	0.042	1.80 (0.32, 3.28)	0.018

SBP - Systolic blood pressure; BMI - Body mass index, T2DM - Type 2 diabetes mellitus; HTT - Hypertension therapy

Discussion

BP from early midlife predicts LVMI and LV remodelling in both men and women and for BP at age 53y, this is independent of current BP (BP at age 60-64y). We identified 43-53y as a potential sensitive period for the development of poor cardiac structure where rapid rises in SBP were particularly detrimental. Those on HTT at all ages had higher LVMI after accounting for current SBP, some of this effect could be accounted for by prior higher BP.

A limited number of studies have investigated the role of high BP in early life on later LV structure. Studies in children and young adults from the Bogalusa[15-17] and CARDIA[18] cohorts and Swedish military recruits[19] have demonstrated a positive relationship between BP and subsequent LVM. Two further studies reported that BP in middle age was positively associated with LVM measured two decades later[20, 21] but neither study took contemporary BP into account and therefore the role of BP *tracking* could not be excluded (those with earlier higher BPs continuing on the same trajectory of BP rise and ending up with higher BP compared to their peers). Our findings, based on multiple longitudinal measurements of BP, suggest that the effects of earlier adult BP are not entirely due to tracking. Notably, BP at 53y was more strongly related to LVMI than BP at 60-64y in a mutually adjusted model. The importance of BP at age 53y may be due to the rapid acceleration in BP typically seen around this period of life.[22] This accords with our findings showing that rapid BP rise between 43-53y has the strongest association with subsequent LVMI. Interestingly, one previous study has suggested that faster rises in BP were associated with increased LVM, but this conclusion was based on measurements over only 2y.[23] In contrast we have analysed rate of change in BP over a 28y period and have divided the time into segments to identify a particularly *sensitive period* for future LVM. Sensitive periods are times when exposure to particular risk factors

may have a greater influence on a subsequent health outcome than would exposure to the same risk factor at a different time.[24] Our data suggests that the period between ~ 40–50y may be such a period.

Current guidelines do not take into account changes in BP when determining whether HTT should be prescribed,[25] even though very rapid rises in BP (e.g. in malignant hypertension) are associated with development of acute cardiological, neurological, renal and ophthalmological problems.[26] Rather, whether BP crosses a threshold is currently of paramount importance. Our finding of greater LVMI in those with a rapid rise in BP in the 5th decade of life was not just driven by individuals becoming hypertensive but held for those whose BP remained in the "normal" range. This suggests a paradigm shift in our evaluation of cardiovascular risk due to BP and would necessitate the identification and appropriate management of individuals exhibiting sharp rises of BP even within the normal BP range. Recent clinical trials have tested whether intervention early in adulthood to prevent the development of hypertension has benefits, with mixed results.[27, 28] Our finding, that those on HTT have higher mean LVMI, even if the BP has been controlled, further highlights the importance of intervention before quickly rising/high BP causes a "legacy" of target organ damage which may not be fully reversed even if BP is subsequently normalized with medication. The current practice in younger individuals of "watching and waiting" until BP crosses 140/90 mm Hg may be detrimental to their health as permanent change in LVMI may have already occurred before treatment initiation.

Strengths and Limitations

The study members remaining in the Medial Research Council National Survey of Health and Development (MRC NSHD) have been found to be representative of native-born adults living in England, Scotland, and Wales at the time of data collection at 53y[29] and at 60-64y.[22] Hence our findings are likely to be generalizable to the British-born population. The repeated measurements of BP in our study, the longest running birth cohort in the UK, allowed us to carry out an analysis investigating the impact of BP tracking and the relative importance of rate of change in BP over different periods of the adult life course.

Missing data are inevitable in studies as long-running as the MRC NSHD.[30] Compared to study members who attended clinic and had echocardiography, those who had examinations at home visits had, on average, greater BMI and higher resting heart rate consistent with previous work showing those who attended clinic were healthier than those who had a home visit.[31] Exclusion of this less healthy group from our analyses could have influenced our findings: it is plausible, that if these individuals had undergone echocardiography, the overall associations between BP and LVM would have been strengthened.

BP was not measured in the MRC NSHD prior to 36y, and hence we were unable to assess whether there are important earlier-life periods. We are also limited to identifying a sensitive period from 3 approximately 10y intervals. Echocardiography was only carried out in the most recent round of data collection and hence the possibility of reverse causality, namely that increased LVMI in early-life results in raised SBP and increased rate of rise in midlife BP cannot be excluded. However, a previous study by Zureik et al,[23] demonstrated that change in BP preceded change in LVMI, suggesting this is an unlikely explanation of our findings.

Conclusions

Higher BP in midlife predicts subsequent higher LVMI and remodelling, independent of current BP for BP at age 53y, with rapid rate of change in the fifth decade playing a key role. People on HTT have higher LVMI than untreated individuals, even when accounting for their higher BP. Together these observations suggest that exposure to high BP and accelerated rise in BP results in irreversible adverse changes in LV structure. Our findings suggest the need for trials to re-evaluate current strategies for monitoring and treating BP in younger adults and to test the benefits of early identification and treatment of those with rapid rises in BP.

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Chapter 5

The effect of midlife blood pressure and midlife rise in blood pressure on future cardiac function

Introduction

With an ageing population, and better post myocardial infarction survival, the burden of congestive heart failure is increasing and represents a major public health challenge.[1] Systolic and diastolic dysfunction can both lead to heart failure and may be different ends of the same continuum.[2, 3] Diastolic dysfunction is common in people over 45 years[1] and is a precursor of heart failure with preserved ejection fraction (HFPEF).[4, 5] Diastolic dysfunction also predicts increased cardiovascular and all-cause mortality in those with normal ejection fractions.[4, 6] Systolic heart failure is as common as diastolic heart failure with at least half the patients diagnosed with heart failure having a reducing ejection fraction (EF).[7] High systolic blood pressure (SBP) is an important cause of diastolic dysfunction and while ischaemic heart disease is the leading cause of systolic heart failure, hypertension is also a major cause.[8] There is also evidence that raised antecedent SBP in early and mid-adulthood is associated with

increased risk of heart failure[9] and elevated risk of cardiovascular mortality independent of current blood pressure (BP).[10, 11] However, there has been limited work investigating the effects of longitudinal changes in BP over adulthood on systolic and diastolic function[12, 13] and the long-term impact of antihypertensive treatment (HTT) remains uncertain.

In this chapter we investigate the effect of earlier BP on future cardiac function (i.e. at age 60-64y) and whether this effect is independent of BP at age 60-64y. We also investigate the effect of HTT from the age of 36y onwards on cardiac function at age 60-64y measured by echocardiography.

Methods

The methods have been described in detail in the methods chapter.

Echocardiography

The following markers of diastolic function were measured in accordance with ASE/EAE recommendations – ratio of early (E) to late (A) transmitral Doppler flow (E/A), early (e') myocardial velocity at the mitral valve annulus (average of septal and lateral wall measures) e', E/e' and ratio of early and late (a') myocardial velocities at the mitral valve annulus (average of septal and lateral wall measures) e'/a'.[14] E/e' was used as the primary measure of diastolic function, as advocated by the latest (2009) joint European Society of Echocardiography and American Society of Echocardiography guidelines,[14] although other

measures (E/A, e' and e'/a') were also examined. Left atrial volume indexed to body surface area (LAVI) was also examined as a marker of chronically elevated left ventricular filling pressures.[15, 16]

Systolic function was assessed by measuring EF [(using Simpson's biplane method or by linear 2D M mode measurements if Simpson's method was not possible[17] as described in the methods chapter (chapter 3)].

Statistical Analysis

Initially, separate regression models investigated the association between SBP at each of the 4 ages at which it was measured and measures of cardiac function at 60-64y, with adjustment for sex, age at clinic visit and clinic attended. We tested whether these associations were linear and whether there was an interaction by gender. There was no gender interaction so in subsequent analyses both genders were pooled and adjusted for sex. HTT at the same age as BP measurement was then added to models. Additional models assessed whether earlier SBP remained predictive once SBP at age 60-64y was also included. Final adjustments were made by including BMI and T2DM at age 60-64y and finally left ventricular mass indexed to body surface area (LVMI).

To investigate whether rate of change in SBP at a particular period of midlife was more strongly associated with diastolic function, a rate of change in BP model was constructed similar to that described in the methods chapter (chapter 3).

Similar analyses were repeated for diastolic BP (DBP), pulse pressure (PP) and mean arterial pressure (MAP).

Sensitivity analyses were carried out to assess whether the associations with SBP remained unchanged if those on HTT or those who were hypertensive (SBP>=140 mmHg and/or DBP >= 90mmHg) were excluded.

Results

Characteristics of participants at age 60-64y relevant to this chapter are shown in table 5.1. Compared to women, men had a higher mean E/e' and a larger mean LAVI. e'/a' was higher in women while there were no sex differences for E/A and e'. Mean EF was higher in women while s' was higher in men.

Table 5.1. Echocardiographic and cardiac risk factor characteristics of study participants.

Unless otherwise stated data refer to age 60-64y.

Variable (at age 60-64y unless stated otherwise)	All		Men		Women	
	n	Result	n	Result	n	Result
Age, y	1472	63.3 (1.1)	696	63.2 (1.1)	776	63.3 (1.1)
BMI, kg/m^2	1480	27.5 (4.6)	701	27.7 (4.0)	779	27.4 (5.1)
SBP, mmHg	1478	135.7 (17.9)	701	139.0 (17.7)	777	132.8 (17.7)
SBP in those on HTT, mmHg	315	137.5 (17.6)	160	139.2 (18.2)	155	135.8 (16.8)
SBP in those not on HTT, mmHg	1011	135.1 (18.0)	457	138.6 (17.4)	554	132.1 (18.0)
SBP at age 53y, mmHg	1393	134.1 (19.1)	657	137.8 (18.9)	736	130.7 (18.7)
SBP at age 43y, mmHg	1381	121.5 (14.5)	654	123.0 (14.3)	727	120.1 (14.6)
SBP at age 36y, mmHg	1334	118.3 (14.0)	631	121.3 (14.2)	703	115.6 (13.4)
DBP, mmHg	1478	77.4 (9.7)	701	79.0 (9.8)	777	75.9 (9.3)
DBP at age 53y, mm Hg	1393	83.4 (11.9)	657	86.2 (11.9)	736	80.9 (11.3)
DBP at age 43y, mm Hg	1381	78.5 (11.3)	654	80.9 (11.2)	727	76.3 (10.9)
DBP at age 36y, mm Hg	1333	76.0 (11.7)	630	77.8 (11.7)	703	74.4 (11.4)
Heart Rate, bpm	1473	68.5 (11.8)	699	67.2 (12.5)	774	69.7 (11.0)
LVMI, g/m^2	1480	95.7 (26.6)	701	104.1 (27.9)	779	88.1 (22.9)
E/A	1424	1.0 (0.3)	668	1.0 (0.3)	756	1.0 (0.3)

e', cm/s	1381	8.8 (1.9)	640	8.9 (1.9)	741	8.7 (1.9)
E/e'	1354	8.0 (2.1)	681	7.5 (2.1)	727	8.3 (2.1)
e'/a'	1358	0.8 (0.2)	624	0.8 (0.2)	734	0.9 (0.2)
LAVI, ml/m^2	1285	20.9 (7.3)	624	21.7 (7.5)	661	20.0 (7.0)
Ejection Fraction (%)	1453	68.7 (9.7)	687	67.2 (10.1)	766	69.9 (9.2)
s' (cm/sec)	1350	7.7 (1.6)	626	8.1 (1.7)	724	7.5 (1.4)
Antihypertensive medication, n (%)	1332	315 (24)	620	159 (26)	712	156 (22)
Type 2 Diabetes Mellitus, n (%)	1357	73 (6)	635	37 (6)	722	36 (5)

Data are mean (SD), or n (%) as appropriate.

BMI - Body mass index; SBP -Systolic blood pressure; DBP -Diastolic blood pressure; LVMI - Left ventricular mass indexed to body surface area; LAVI - Left atrial volume indexed to body surface area

The association between SBP at various ages and diastolic function was assessed (Tables 5.2a-e).

SBP from 36y onwards was positively associated with increased E/e' (Table 5.2a). The relationship persisted after adjustment for age, sex, clinic attended and current HTT/SBP/BMI/presence of T2DM. Analyses were repeated replacing SBP with DBP, MAP or PP (Tables 5.2h-j). The relationships of these BP measures with E/e' were qualitatively broadly similar to SBP with DBP/PP/MAP at age 36y positively associated with E/e' at 60-64y in the minimally adjusted model. On full adjustment, DBP from 43y, PP at 60-64y and MAP from 43y were positively associated with E/e'.

From 43y onwards, those on HTT had increased E/e'; this was not affected substantively by adjustment for current SBP; regression coefficients were slightly attenuated by adjustment for T2DM and BMI, although relationships remained statistically significant (Table 5.2a). We also investigated whether the effect of earlier SBP was mediated via left ventricular (LV) hypertrophy (LVH) by the inclusion of LVMI in the regression models. This was not the case (Table 5.2a).

We investigated whether relationships between elevated BP in earlier life and E/e' might be driven by inclusion of people who went on to develop hypertension. However, when those who were hypertensive at 60-64y (SBP>=140 mmHg and/or DBP >= 90mmHg) were excluded from the analysis, the associations remained very similar (Table 5.2f).

Analyses were also repeated after excluding those on HTT; despite the reduced number of individuals in this sub-analysis, SBP from 36y onwards remained positively predictive of E/e' (Table 5.2g).

Qualitatively similar findings were observed when the associations between current and antecedent SBP and E/A or LAVI were examined, although relationships tended to be weaker. Only SBP at 53y was predictive of future E/A, and HTT at any age was unrelated to E/A (Table 5.2b). SBP at age 53y and HTT at ages 53y and 60-64y were associated with LAVI (Table 5.2c). Data relating SBP measured at various ages to e' and e'/a' are shown in Tables 2d-e. Overall associations were qualitatively similar to those for E/A.

The associations between DBP, PP and MAP and E/e' were also examined (Tables 5.2h-j). The overall associations were qualitatively similar to those between SBP and E/e'.

The association between SBP at the various ages and systolic function was also examined (Tables 5.2k-l).

SBP was not associated with EF in the minimally adjusted models (Table 5.2k). On further adjustment SBP remained unrelated to EF except at age 53y. SBP at age 53y was not associated with EF on minimal adjustment or after including HTT in the model. However on further adjustment for SBP at 60-64y, the effect size increased slightly and the effect became significant (increase in SBP associated with increase in EF i.e. better systolic function). With further adjustment for T2DM and BMI at age 60-64y, the effect size marginally increased and significance remained. HTT was not associated with EF.

Only SBP at age 36y was associated with s'. Increased SBP at age 36y was associated with decreased s' (i.e. poorer systolic function). This remained the case after the sequential adjustments with a marginal attenuation of effect size with the adjustments. Only HTT at age 53y was associated with s', with the association being negative (i.e. poorer systolic function).

The strength of the effect was similar with sequential adjustments with a marginal increase on the addition of T2DM and SBP at age 60-64y and then on the inclusion of LVMI.

Table 5.2a. Regression coefficients, 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on E/e' at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)		Model 5 (model 4 + LVMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y	**SBP**	0.019 (0.010, 0.029)	<0.001	0.019 (0.010, 0.029)	<0.001	0.012 (0.002, 0.021)	0.015	0.012 (0.003, 0.022)	0.010	0.010 (0.001, 0.020)	0.038
(n = 1196)	***HTT***	-	-	*-0.05 (-1.21, 1.11)*	*0.933*	*0.10 (-1.04, 1.24)*	*0.868*	*-0.09 (-1.21, 1.04)*	*0.880*	*-0.07 (-1.19, 1.04)*	*0.898*
Age 43y	**SBP**	0.020 (0.011, 0.028)	<0.001	0.018 (0.010, 0.027)	<0.001	0.009 (0.000, 0.018)	0.049	0.010 (0.001, 0.018)	0.031	0.009 (-0.0001, 0.018)	0.054
(n = 1221)	***HTT***	-	-	*1.46 (0.68, 2.23)*	*<0.001*	*1.46 (0.68, 2.23)*	*<0.001*	*1.15 (0.38, 1.93)*	*0.003*	*1.00 (0.18, 1.81)*	*0.017*
Age 53y	**SBP**	0.024 (0.018, 0.030)	<0.001	0.022 (0.016, 0.028)	<0.001	0.015 (0.008, 0.021)	<0.001	0.013 (0.006, 0.019)	<0.001	0.010 (0.003, 0.017)	0.004
(n = 1293)	***HTT***	-	-	*0.77 (0.42, 1.11)*	*<0.001*	*0.77 (0.43, 1.11)*	*<0.001*	*0.64 (0.30, 0.98)*	*<0.001*	*0.55 (0.18, 0.92)*	*0.003*
Age 60-64y	**SBP**	0.025 (0.019, 0.031)	<0.001	0.025 (0.018, 0.031)	<0.001	-	-	0.022 (0.016, 0.028)	<0.001	0.021 (0.014, 0.027)	<0.001
(n = 1299)	***HTT***	-	-	*0.76 (0.49, 1.02)*	*<0.001*	-	-	*0.59 (0.31, 0.86)*	*<0.001*	*0.43 (0.15, 0.70)*	*0.003*

HTT - Hypertension treatment; SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

Table 5.2b. Regression coefficients, 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on E/A at 60-64years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)		Model 5 (model 4 + LVMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y	**SBP**	0.000070 (-0.0012, 0.0013)	0.913	0.000040 (-0.0012, 0.0013)	0.950	0.00071 (-0.0006, 0.0020)	0.282	0.00052 (-0.0074, 0.0018)	0.419	0.0007 (-0.0007, 0.0020)	0.324
(n = 1267)	***HTT***	-	-	*0.064 (-0.096, 0.225)*	*0.431*	*0.051 (-0.108, 0.210)*	*0.529*	*0.082 (-0.074, 0.238)*	*0.305*	*0.079 (-0.080, 0.238)*	*0.328*
Age 43y	**SBP**	0.00010 (-0.0010, 0.0013)	0.858	0.00017 (-0.0098, 0.0013)	0.776	0.0012 (-0.0001, 0.0024)	0.052	0.0097 (-0.0002, 0.0022)	0.109	0.0006 (-0.0007, 0.0018)	0.362
(n = 1296)	***HTT***	-	-	*-0.064 (-0.169, 0.040)*	*0.227*	*-0.066 (-0.170, 0.037)*	*0.209*	*-0.025 (-0.128, 0.077)*	*0.628*	*-0.020 (-0.130, 0.090)*	*0.719*
Age 53y	**SBP**	-0.0015 (-0.0023, -0.0007)	<0.001	-0.0016 (-0.0024, -0.0008)	<0.001	-0.00095 (-0.0018, -0.0007)	0.035	-0.0067 (-0.0015, 0.0002)	0.131	-0.0007 (-0.0016, 0.0003)	0.169
(n = 1369)	***HTT***	-	-	*0.032 (-0.015, 0.078)*	*0.180*	*0.029 (-0.017, 0.076)*	*0.214*	*0.042 (-0.004, 0.089)*	*0.072*	*0.038 (-0.013, 0.088)*	*0.143*
Age 60-64y	**SBP**	-0.0021 (-0.0029, -0.0012)	<0.001	-0.0020 (-0.0029, -0.0012)	<0.001	-	-	-0.0016 (-0.0025, -0.0008)	<0.001	-0.0015 (-0.0023, -0.0006)	0.001
(n = 1375)	***HTT***	-	-	*-0.023 (-0.059, 0.013)*	*0.216*	-	-	*0.0016 (-0.0350, 0.0382)*	*0.933*	*-0.001 (-0.039, 0.038)*	*0.976*

HTT - Hypertension treatment; SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

Table 5.2c. Regression coefficients (β, ml/m^2), 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on left atrial volume indexed to body surface area at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y	**SBP**	0.033 (0.001, 0.065)	0.041	0.032 (-0.0002, 0.0633)	0.052	0.026 (-0.007, 0.058)	0.119	0.027 (-0.0045, 0.059)	0.093
(n = 1140)	***HTT***	-	-	*3.728 (-0.563, 8.019)*	*0.089*	*3.890 (-0.392 8.191)*	*0.075*	*2.785 (-1.452, 7.021)*	*0.197*
Age 43y	**SBP**	0.033 (0.003, 0.062)	0.029	0.031 (0.001, 0.060)	0.042	0.026 (-0.005, 0.057)	0.103	0.027 (-0.003, 0.058)	0.078
(n = 1164)	***HTT***	-	-	*2.830 (0.210, 5.449)*	*0.034*	*-2.849 (0.229, 5.469)*	*0.033*	*1.595 (-1.018, 4.208)*	*0.231*
Age 53y	**SBP**	0.051 (0.030, 0.072)	<0.001	0.043 (0.022, 0.064)	<0.001	0.043 (0.019, 0.066)	<0.001	0.036 (0.013, 0.059)	0.002
(n = 1189)	***HTT***	-	-	*2.333 (1.119,3.547)*	*<0.001*	*2.336 (1.120, 3.552)*	*<0.001*	*1.872 (0.650, 3.094)*	*0.003*
Age 60-64y	**SBP**	0.024 (0.002, 0.046)	0.033	0.021 (-0.0005, 0.043)	0.056	-	-	0.012 (-0.010, 0.034)	0.297
(n = 1248)	***HTT***	-	-	*1.728 (0.822, 2.632)*	*<0.001*	-	-	*1.093 (0.166, 0.345)*	*0.021*

HTT - Hypertension treatment; SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

Table 5.2d. Regression coefficients, 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on e' at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)		Model 5 (model 4 + LVMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y (n = 1227)	**SBP**	-0.008 (-0.017, 0.000)	0.061	-0.008 (-0.017, 0.000)	0.062	-0.003 (-0.011, 0.006)	0.540	-0.004 (-0.012, 0.005)	0.418	-0.003 (-0.012, 0.006)	0.566
	HTT	-	-	*-0.026 (-1.094, 1.042)*	*0.962*	*-0.133 (-1.190, 0.924)*	*0.805*	*0.005 (-1046, 1.056)*	*0.993*	*0.005 (-1.037, 1.047)*	*0.992*
Age 43y (n = 1255)	**SBP**	-0.007 (-0.015, 0.001)	0.082	-0.006 (-0.014, 0.002)	0.115	0.002 (-0.007, 0.010)	0.718	0.001 (-0.008, 0.009)	0.900	-0.0002 (-0.009, 0.008)	0.959
	HTT	-	-	*-0.794 (-1.511, -0.076)*	*0.030*	*-0.769 -(1.479, -0.060)*	*0.034*	*-0.602 (-1.313, 0.109)*	*0.097*	*-0.393 (-1.158, 0.371)*	*0.313*
Age 53y (n = 1329)	**SBP**	-0.013 (-0.018, -0.007)	<0.001	-0.012 (-0.017, -0.006)	<0.001	-0.006 (-0.012, -0.000)	0.038	-0.005 (-0.011, 0.0001)	0.092	-0.004 (-0.010, 0.003)	0.276
	HTT	-	-	*-0.284 (-0.601, 0.033)*	*0.079*	*-0.284 (-0.599, 0.030)*	*0.076*	*-0.234 (-0.551, 0.083)*	*0.148*	*-0.190 (-0.532, 0.153)*	*0.278*
Age 60-64y (n = 1335)	**SBP**	-0.018 (-0.024, -0.012)	<0.001	-0.017 (-0.023, -0.011)	<0.001	-	-	-0.016 (-0.021, -0.010)	<0.001	-0.014 (-0.020, -0.008)	<0.001
	HTT	-	-	*-0.271 (-0.517, -0.026)*	*0.030*	-	-	*-0.162 (-0.041, 0.089)*	*0.206*	*-0.081 (-0.341, 0.179)*	*0.541*

HTT - Hypertension treatment; SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

Table 5.2e. Regression coefficients, 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on e'/a' at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)		Model 5 (model 4 + LVMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y	**SBP**	-0.0004 (-0.0015, 0.0006)	0.437	-0.00044 (-0.0015, 0.0006)	0.414	0.00033 (-0.0007, 0.0014)	0.540	0.00018 (-0.00086, 0.00123)	0.735	0.0003 (-0.0008, 0.0013)	0.643
(n = 1209)	***HTT***	-	-	*0.044 (-0.086, 0.173)*	*0.508*	*0.028 (-0.099, 0.156)*	*0.661*	*0.054 (-0.071, 0.180)*	*0.398*	*0.052 (-0.073, 0.177)*	*0.413*
Age 43y	**SBP**	-0.00047 (-0.0014, 0.0005)	0.328	-0.00040 (-0.0014, 0.0006)	0.409	0.00070 (-0.0003, 0.0017)	0.167	0.0053 (-0.0005, 0.0015)	0.292	0.0005 (-0.0006, 0.0015)	0.374
(n = 1255)	***HTT***	-	-	*-0.090 (-0.177, -0.003)*	*0.042*	*-0.087 (-0.172, -0.001)*	*0.047*	*-0.052 (-0.137, 0.033)*	*0.229*	*-0.029 (-0.121, 0.063)*	*0.537*
Age 53y	**SBP**	-0.0017 (-0.0023, -0.0010)	<0.001	-0.0017 (-0.0024, -0.0010)	<0.001	-0.00099 (-0.0017, -0.0003)	0.008	-0.00072 (-0.0015, 0.0001)	0.051	-0.0006 (0.0014, 0.0001)	0.105
(n = 1308)	***HTT***	-	-	*0.0057 (-0.0333, 0.0447)*	*0.774*	*0.0061 (-0.0326, 0.0449)*	*0.756*	*0.020 (-0.018, 0.059)*	*0.300*	*0.029 (-0.012, 0.070)*	*0.168*
Age 60-64y	**SBP**	-0.0023 (-0.0030, -0.0016)	<0.001	-0.0022 (-0.0029, -0.0015)	<0.001	-	-	-0.0018 (-0.0025, -0.0011)	<0.001	-0.0018 (-0.0025, -0.0010)	<0.001
(n = 1314)	***HTT***	-	-	*-0.017 (-0.047, 0.013)*	*0.265*	-	-	*0.006 (-0.003, 0.037)*	*0.688*	*0.007 (-0.025, 0.038)*	*0.676*

HTT - Hypertension treatment; SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

Table 5.2f. Regression coefficients, 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on E/e' at 60-64 years excluding those who were hypertensive (SBP>=140 mmHg and/or DBP >= 90mmHg).

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)		Model 5 (model 4 + LVMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y	**SBP**	0.017 (0.0056, 0.0285)	0.004	0.017 (0.0056, 0.0285)	0.004	0.0082 (-0.0034, 0.0197)	0.165	0.0083 (-0.0031, 0.0198)	0.153	0.0079 (-0.0040, 0.0199)	0.194
(n = 1064)	***HTT***	-	-	*1.14 (-0.36, 2.64)*	*0.136*	*1.23 (-0.24, 2.70)*	*0.101*	*0.93 (-0.53,2.39)*	*0.212*	*0.91 (-0.55, 2.36)*	*0.222*
Age 43y	**SBP**	0.014 (0.017, 0.026)	0.026	0.012 (0.0002, 0.0245)	0.046	-0.000093 (-0.012, 0.012)	0.988	0.0016 (-0.011, 0.014)	0.803	0.0033 (-0.0095, 0.0162)	0.610
(n = 1012)	***HTT***	-	-	*2.06 (1.06,3.06)*	*<0.001*	*1.97(0.99, 2.95)*	*<0.001*	*1.68 (0.70, 2.67)*	*0.001*	*1.62 (0.60, 2.63)*	*0.002*
Age 53y	**SBP**	0.028 (0.015, 0.040)	<0.001	0.027 (0.015, 0.039)	<0.001	0.013 (0.0035, 0.0265)	0.044	0.013 (-0.0048, 0.0257)	0.059	0.014 (0.003, 0.027)	0.045
(n = 769)	***HTT***	-	-	*0.66 (0.17, 1.14)*	*0.008*	*0.57(0.096, 1.053)*	*0.019*	*0.52 (0.04, 1.00)*	*0.034*	*0.36 (-0.16, 0.88)*	*0.174*
Age 60-64y	**SBP**	0.036 (0.023, 0.049)	<0.001	0.034 (0.021, 0.047)	<0.001	-	-	0.029 (0.016, 0.042)	<0.001	0.028 (0.014, 0.042)	<0.001
(n = 802)	***HTT***	-	-	*0.94 (0.60, 1.28)*	*<0.001*	-	-	*0.67 (0.32, 1.02)*	*<0.001*	*0.58 (0.21, 0.95)*	*0.002*

HTT - Hypertension treatment; SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

Table 5.2g. Regression coefficients, 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on E/e' at 60-64 years excluding those who were on HTT.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)		Model 5 (model 4 + LVMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y	**SBP**	0.020 (0.011, 0.029)	<0.001	0.020 (0.011, 0.029)	<0.001	0.012 (0.0025, 0.0215)	0.013	0.012 (0.0029, 0.0217)	0.010	0.011 (0.0014, 0.0211)	0.025
(n = 1205)	***HTT***	-	-	-	-	-	-	-	-	-	-
Age 43y	**SBP**	0.019 (0.011, 0.028)	<0.001	0.019 (0.011, 0.028)	<0.001	0.010 (0.00082, 0.01822)	0.032	0.010 (0.0014, 0.0186)	0.023	0.010 (0.00083, 0.01906)	0.032
(n = 1217)	***HTT***	-	-	-	-	-	-	-	-	-	-
Age 53y	**SBP**	0.020 (0.013, 0.026)	<0.001	0.020 (0.013, 0.026)	<0.001	0.012 (0.0050, 0.0192)	0.001	0.010 (0.0033, 0.0175)	0.004	0.0086 (0.0012, 0.0161)	0.024
(n = 1113)	***HTT***	-	-	-	-	-	-	-	-	-	-
Age 60-64y	**SBP**	0.026 (0.020, 0.033)	<0.001	0.026 (0.020, 0.033)	<0.001	-	-	0.024 (0.017, 0.030)	<0.001	0.024 (0.017, 0.031)	<0.001
(n = 1030)	***HTT***	-	-	-	-	-	-	-	-	-	-

HTT - Hypertension treatment; SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

Table 5.2h. Regression coefficients, 95% confidence intervals and p values estimating the effect of DBP and HTT at 4 time points on E/e' at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + DBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)		Model 5 (model 4 + LVMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y	**DBP**	0.018 (0.0054, 0.0302)	0.005	0.018 (0.0054, 0.0302)	0.005	0.012 (-0.0007, 0.0246)	0.064	0.011 (-0.0011, 0.0238)	0.074	0.010 (-0.0026, 0.0236)	0.116
(n = 1215)	***HTT***	-	-	*-0.029 (-1.187, 1.129)*	*0.961*	*0.046 (-1.106, 1.197)*	*0.938*	*-0.124 (-1.261,1.012)*	*0.830*	*-0.150 (-1.281, 0.981)*	*0.795*
Age 43y	**DBP**	0.023 (0.011, 0.036)	<0.001	0.021 (0.0082, 0.0333)	0.001	0.016 (0.0028, 0.0284)	0.017	0.013 (0.00062, 0.0259)	0.040	0.014 (0.00081, 0.0279)	0.038
(n = 1242)	***HTT***	-	-	*1.421 (0.618, 2.224)*	*0.001*	*1.389 (0.589, 2.189)*	*0.001*	*1.059 (0.264, 1.854)*	*0.009*	*0.904 (0.078, 1.731)*	*0.032*
Age 53y	**DBP**	0.032 (0.022, 0.042)	<0.001	0.028 (0.019, 0.038)	<0.001	0.022 (0.012, 0.033)	<0.001	0.017 (0.0067, 0.0279)	0.001	0.017 (0.0060, 0.0284)	0.003
(n = 1265)	***HTT***	-	-	*0.859 (0.515, 1.203)*	*<0.001*	*0.858 (0.515, 1.202)*	*<0.001*	*0.696 (0.0351, 1.040)*	<0.001	*0.575 (0.206, 0.944)*	*0.002*
Age 60-64y	**DBP**	0.029 (0.018, 0.041)	<0.001	0.027 (0.016, 0.039)	<0.001	-	-	0.025 (0.013, 0.036)	<0.001	0.022 (0.010, 0.034)	<0.001
(n = 1331)	***HTT***	-	-	*0.788 (0.016, 0.039)*	*<0.001*	-	-	*0.588 (0.321, 0.855)*	*<0.001*	*0.440 (0.010, 0.034)*	*<0.001*

HTT - Hypertension treatment; DBP - Diastolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

Table 5.2i. Regression coefficients, 95% confidence intervals and p values estimating the effect of PP and HTT at 4 time points on E/e' at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + PP at 60-64y)		Model 4 (model 3 + T2DM + BMI)		Model 5 (model 4 + LVMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y	**PP**	0.016 (0.0033, 0.0279)	0.013	0.016 (0.0033, 0.0279)	0.013	0.010 (-0.0019, 0.0227)	0.097	0.011 (-0.0009, 0.0234)	0.069	0.0099 (-0.0027, 0.0224)	0.123
(n = 1215)	***HTT***	-	-	*0.122 (-1.033, 1.277)*	*0.835*	*0.203 (-0.935, 1.341)*	*0.727*	*0.027 (-1.100,1.153)*	*0.962*	*-0.005 (-1.125, 1.115)*	*0.993*
Age 43y	**PP**	0.016 (0.0043, 0.0270)	0.007	0.016 (0.0047, 0.0273)	0.006	0.0054 (-0.0062, 0.0170)	0.364	0.0075 (-0.0040, 0.0190)	0.199	0.0067 (-0.0054, 0.0188)	0.278
(n = 1242)	***HTT***	-	-	*1.587 (0.787, 2.386)*	*<0.001*	*1.548 (0.762, 2.334)*	*<0.001*	*1.231 (0.447, 2.016)*	*0.002*	*0.904 (0.078, 1.731)*	*0.032*
Age 53y	**PP**	0.024 (0.016, 0.033)	<0.001	0.021 (0.012, 0.030)	<0.001	0.013 (0.0038, 0.022)	0.006	0.011 (0.0022, 0.0204)	0.015	0.0091 (-0.0004, 0.0186)	0.059
(n = 1265)	***HTT***	-	-	*0.890 (0.545, 1.235)*	*<0.001*	*0.877 (0.536, 1.22)*	*<0.001*	*0.714 (0.371, 1.057)*	<0.001	*0.620 (0.254, 0.986)*	*0.001*
Age 60-64y	**PP**	0.030 (0.022, 0.038)	<0.001	0.028 (0.020, 0.036)	<0.001	-	-	0.025 (0.013, 0.036)	<0.001	0.024 (0.016, 0.033)	<0.001
(n = 1331)	***HTT***	-	-	*0.749 (0.490, 1.009)*	*<0.001*	-	-	*0.025 (0.017, 0.033)*	*<0.001*	*0.427 (0.147, 0.707)*	*0.003*

HTT - Hypertension treatment; PP - Pulse pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

Table 5.2j. Regression coefficients, 95% confidence intervals and p values estimating the effect of MAP and HTT at 4 time points on E/e' at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + MAP at 60-64y)		Model 4 (model 3 + T2DM + BMI)		Model 5 (model 4 + LVMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y	**MAP**	0.022 (0.010, 0.034)	<0.001	0.022 (0.010, 0.034)	<0.001	0.013 (0.0004, 0.0252)	0.044	0.013 (0.0005, 0.0251)	0.041	0.012 (-0.0012, 0.0246)	0.076
(n = 1215)	***HTT***	-	-	*-0.029 (-1.187, 1.129)*	*0.961*	*0.046 (-1.106, 1.197)*	*0.938*	*-0.092 (-1.221,1.037)*	*0.873*	*0.91 (-0.55, 2.36)*	*0.222*
Age 43y	**MAP**	0.026 (0.014, 0.038)	<0.001	0.024 (0.012, 0.036)	<0.001	0.015 (0.0024, 0.0266)	0.019	0.013 (0.0015, 0.0254)	0.027	0.014 (0.0011, 0.0267)	0.033
(n = 1242)	***HTT***	-	-	*1.407 (0.606, 2.207)*	*0.001*	*1.370 (0.579, 2.161)*	*0.001*	*1.058 (0.269, 1.846)*	*0.009*	*0.904 (0.078, 1.731)*	*0.032*
Age 53y	**MAP**	0.033 (0.025, 0.042)	<0.001	0.030 (0.021, 0.038)	<0.001	0.021 (0.011, 0.030)	<0.001	0.017 (0.0070, 0.0261)	0.001	0.016 (0.0056, 0.0258)	0.002
(n = 1265)	***HTT***	-	-	*0.797 (0.453, 1.142)*	*<0.001*	*0.800 (0.458, 1.141)*	*<0.001*	*0.658 (0.315, 1.001)*	<0.001	*0.547 (0.179, 0.914)*	*0.004*
Age 60-64y	**MAP**	0.035 (0.025, 0.044)	<0.001	0.033 (0.023, 0.042)	<0.001	-	-	0.030 (0.020, 0.039)	<0.001	0.028 (0.018, 0.038)	<0.001
(n = 1331)	***HTT***	-	-	*0.755 (0.496, 1.015)*	*<0.001*	-	-	*0.573 (0.307, 0.838)*	*<0.001*	*0.432 (0.152, 0.712)*	*0.003*

HTT - Hypertension treatment; MAP – Mean arterial blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

Table 5.2k. Regression coefficients, 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on ejection fraction at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)		Model 5 (model 4 + LVMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y	**SBP**	0.0018 (-0.041, 0.045)	0.936	0.0028 (-0.040, 0.046)	0.898	0.0067 (-0.038, 0.051)	0.766	0.0077 (-0.037, 0.052)	0.733	0.0081 (-0.037, 0.053)	0.723
(n = 1193)	***HTT***	-	-	*-2.321 (-7.734, 3.091)*	*0.400*	*-2.400 (-7.818, 3.017)*	*0.385*	*-2.27 (-7.700, 3.159)*	*0.412*	*-2.263 (-7.700, 3.169)*	*0.414*
Age 43y	**SBP**	0.0000006 (-0.040, 0.040)	1.000	-0.00066 (-0.041, 0.039)	0.974	0.0034 (-0.039, 0.046)	0.874	0.0040 (-0.038, 0.046)	0.854	0.0037 (-0.039, 0.047)	0.865
(n = 1228)	***HTT***	-	-	*0.984 (-2.606, 4.574)*	*0.591*	*0.983 (-2.609, 4.574)*	*0.592*	*1.275 (-2.354, 4.904)*	*0.491*	*0.759 (-2.943, 4.460)*	*0.688*
Age 53y	**SBP**	0.021 (-0.0077, 0.0490)	0.153	0.025 (-0.0040, 0.0542)	0.091	0.035 (0.0029, 0.0664)	0.032	0.038 (0.0065, 0.0704)	0.019	0.038 (0.0056, 0.0705)	0.022
(n = 1248)	***HTT***	-	-	*-1.131 (-2.786, 0.525)*	*0.180*	*-1.157 (-2.812, 0.498)*	*0.170*	*-0.826 (-2.512, 0.860)*	*0.337*	*-0.783 (-2.493, 0.928)*	*0.370*
Age 60-64y	**SBP**	-0.0060 (-0.035, 0.235)	0.692	-0.0064 (-0.036, 0.231)	0.669	-	-	-0.0038 (-0.034, 0.026)	0.804	-0.0055 (-0.036, 0.025)	0.721
(n = 1309)	***HTT***	-	-	*0.307 (-0.933, 1.548)*	*0.627*	-	-	*0.526 (-0.758, 1.809)*	*0.422*	*0.473 (-0.831, 1.776)*	*0.477*

HTT - Hypertension treatment; SBP – Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

Table 5.2l. Regression coefficients, 95% confidence intervals and p values estimating the effect of SBP and HTT at 4 time points on s' at 60-64 years.

Variable		Model 1 (age sex, clinic)		Model 2 (Model 1 + HTT)		Model 3 (model 2 + SBP at 60-64y)		Model 4 (model 3 + T2DM + BMI)		Model 5 (model 4 + LVMI)	
		β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
Age 36y	**SBP**	-0.0125 (-0.0196, -0.0054)	0.001	-0.0124 (-0.0195, -0.0053)	0.001	-0.0118 (-0.0191, -0.0044)	0.002	-0.0115 (-0.0189, -0.0042)	0.002	-0.0113 (-0.0189, -0.0037)	0.004
(n = 1223)	***HTT***	-	-	*-0.203 (-1.095, 0.689)*	*0.655*	*-0.214 (-1.107, 0.678)*	*0.638*	*-0.260 (-1.153, 0.634)*	*0.569*	*-0.241 (-1.121, 0.639)*	*0.591*
Age 43y	**SBP**	-0.0046 (-0.0111, 0.0019)	0.169	-0.0044 (-0.0110, 0.0021)	0.183	-0.0030 (-0.0099, 0.0039)	0.397	-0.0028 (-0.0097, 0.0042)	0.433	-0.0032 (-0.0105, 0.00410	0.391
(n = 1242)	***HTT***	-	-	*-0.241 (-0.838, 0.357)*	*0.429*	*-0.234 (-0.832, 0.364)*	*0.443*	*-0.320 (-0.923, 0.284)*	*0.299*	*-0.369 (-1.000, 0.261)*	*0.251*
Age 53y	**SBP**	-0.0018 (-0.0065, 0.0028)	0.446	-0.00082 (-0.0055, 0.0039)	0.732	0.00074 (-0.0044, 0.0059)	0.777	0.00025 (-0.0049, 0.0054)	0.925	0.0011 (-0.0043, 0.0066)	0.691
(n = 1276)	***HTT***	-	-	*-0.311 (-0.579, -0.042)*	*0.023*	*-0.309 (-0.578, -0.041)*	*0.024*	*-0.335 (-0.608, -0.063)*	*0.016*	*-0.339 (-0.630, -0.047)*	*0.023*
Age 60-64y	**SBP**	-0.0042 (-0.0090, 0.0005)	0.081	-0.0041 (-0.0089, 0.0007)	0.092	-	-	-0.0047 (-0.0096, 0.0001)	0.055	-0.0039 (-0.0090, 0.0011)	0.129
(n = 1343)	***HTT***	-	-	*-0.074 (-0.277, 0.129)*	*0.476*	-	-	*-0.114 (-0.324, 0.095)*	*0.284*	*-0.063 (-0.284, 0.157)*	*0.574*

HTT - Hypertension treatment; SBP – Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index; LVMI - Left ventricular mass indexed to body surface area

We looked to see whether there was a sensitive period when rate of change in SBP had the most influence on cardiac function. For diastolic function, increased rate of rise in SBP at all age periods (36-43y, 43-53y and 53-60/64y) was associated with increased E/e' (Table 5.3a), although the relationship was strongest over the period 43-53y. Increased rates of rise in SBP over the age periods 43-53y and 53-60/64y were also significantly associated with decreased E/A (Table 5.3b), while rate of rise in the 43-53y period was also associated with increased LAVI (Table 5.3c).

The associations between rate of change in SBP and future e' (Table 5.3d) and e'/a' (Table 5.3e) were similar to those between rate of SBP change and E/A.

When the associations between rate of change in SBP and systolic function were examined, only rate of change in SBP over 43y-53y was positively associated with EF (i.e. better systolic function) in the fully adjusted model. In the minimally adjusted model, the effect size was less and the effect was marginally non-significant ($p = 0.058$). The effect sizes were much smaller and non-significant for rate of change between 36-43y. There was a reversal of association for rate of change in SBP over 53y-60/64y (i.e. the coefficients were negative indicating worse systolic function); however the associations were just non-significant.

Rate of change in SBP was not associated with s'.

Table 5.3a. Regression coefficients (β, E/e' unit per unit SD change), 95% confidence intervals, and p values for a model showing effect of rate of change in SBP over 3 time periods (36-43y), (43-53y) and (53-60/64y) on E/e' at age 60-64y. Initial model adjusted for sex, age at clinic attendance and clinic attended. Final model also adjusted for BMI, T2DM and HTT.

Period of rate of change in SBP	Adjusted for sex, clinic attended and age		Also adjusted for BMI, T2DM and current HTT	
	β (95%CI)	p value	β (95%CI)	p value
36y – 43y	0.22 (0.09, 0.34)	0.001	0.14 (0.01, 0.27)	0.032
43y – 53y	0.37 (0.25, 0.49)	<0.001	0.23 (0.11, 0.36)	<0.001
53y – 60/64y	0.25 (0.13, 0.37)	<0.001	0.28 (0.16, 0.40)	<0.001

SBP – Systolic blood pressure; BMI – body mass index; T2DM – type 2 diabetes mellitus; HTTT – hypertension treatment

Table 5.3b. Regression coefficients (β, E/A unit per unit SD change), 95% confidence intervals, and p values for a model showing effect of rate of change in SBP over 3 time periods (36-43y), (43-53y) and (53-60/64y) on E/A at age 60-64y. Initial model adjusted for sex, age at clinic attendance and clinic attended. Final model also adjusted for BMI, T2DM and HTT.

Period of rate of change in SBP	Adjusted for sex, clinic attended and age		Also adjusted for BMI, T2DM and current HTT	
	β Coefficient (95%CI)	p value	β Coefficient (95%CI)	p value
36y – 43y	0.003 (-0.014, 0.021)	0.703	0.001 (-0.016, 0.019)	0.879
43y – 53y	-0.032 (-0.049, -0.016)	<0.001	-0.025 (-0.042, -0.008)	0.005
53y – 60/64y	-0.033 (-0.049, -0.016)	<0.001	-0.026 (-0.042, -0.009)	0.002

SBP – Systolic blood pressure; BMI – body mass index; T2DM – type 2 diabetes mellitus; HTTT – hypertension treatment

Table 5.3c. Regression coefficients (β, LAVI unit per unit SD change), 95% confidence intervals, and p values for a model showing effect of rate of change in SBP over 3 time periods (36-43y), (43-53y) and (53-60/64y) on left atrial volume indexed to body surface area at age 60-64y. Initial model adjusted for sex, age at clinic attendance and clinic attended. Final model also adjusted for BMI, T2DM and HTT.

Period of rate of change in SBP	Adjusted for sex, clinic attended and age		Also adjusted for BMI, T2DM and current HTT	
	β Coefficient (95%CI)	p value	β Coefficient (95%CI)	p value
36y – 43y	0.330 (-0.125, 0.785)	0.155	0.260 (-0.207, 0.728)	0.274
43y – 53y	0.893 (0.453, 1.333)	<0.001	0.605 (0.151, 1.059)	0.009
53y – 60/64y	-0.026 (-0.451, 0.399)	0.904	-0.141 (-0.570, 0.287)	0.518

LAVI – left atrial volume indexed to body surface area; SBP – Systolic blood pressure; BMI – body mass index; T2DM – type 2 diabetes mellitus; HTTT – hypertension treatment

Table 5.3d. Regression coefficients, 95% confidence intervals, and p values for a model showing effect of rate of change in SBP over 3 time periods (36-43y), (43-53y) and (53-60/64y) on e' at age 60-64y. Initial model adjusted for sex, age at clinic attendance and clinic attended. Final model also adjusted for BMI, T2DM and HTT.

Period of rate of change in SBP	Adjusted for sex, clinic attended and age		Also adjusted for BMI, T2DM and current HTT	
	β Coefficient (95%CI)	p value	β Coefficient (95%CI)	p value
36y – 43y	-0.07 (-0.19, 0.05)	0.232	-0.05 (-0.17, 0.07)	0.443
43y – 53y	-0.21 (-0.32, -0.10)	<0.001	-0.14 (-0.26, -0.02)	0.021
53y – 60/64y	-0.23 (-0.34, -0.12)	<0.001	-0.22 (-0.33, -0.11)	<0.001

SBP – Systolic blood pressure; BMI – body mass index; T2DM – type 2 diabetes mellitus; HTTT – hypertension treatment

Table 5.3e. Regression coefficients, 95% confidence intervals, and p values for a model showing effect of rate of change in SBP over 3 time periods (36-43y), (43-53y) and (53-60/64y) on e'/a' at age 60-64y. Initial model adjusted for sex, age at clinic attendance and clinic attended. Final model also adjusted for BMI, T2DM and HTT.

Period of rate of change in SBP	Adjusted for sex, clinic attended and age		Also adjusted for BMI, T2DM and current HTT	
	β Coefficient (95%CI)	p value	β Coefficient (95%CI)	p value
36y – 43y	-0.0030 (-0.017, 0.011)	0.675	-0.0039 (-0.018, 0.011)	0.596
43y – 53y	-0.035 (-0.048, -0.021)	<0.001	-0.025 (-0.039, -0.011)	<0.001
53y – 60/64y	-0.033 (-0.046, -0.019)	<0.001	-0.028 (-0.041, -0.014)	<0.001

SBP – Systolic blood pressure; BMI – body mass index; T2DM – type 2 diabetes mellitus; HTTT – hypertension treatment

Table 5.3f. Regression coefficients, 95% confidence intervals, and p values for a model showing effect of rate of change in SBP over 3 time periods (36-43y), (43-53y) and (53-60/64y) on ejection fraction at age 60-64y. Initial model adjusted for sex, age at clinic attendance and clinic attended. Final model also adjusted for BMI, T2DM and HTT.

Period of rate of change in SBP	Adjusted for sex, clinic attended and age		Also adjusted for BMI, T2DM and current HTT	
	β Coefficient (95%CI)	p value	β Coefficient (95%CI)	p value
36y – 43y	0.0015 (-0.6114, 0.6144)	0.996	0.0786 (-0.5541, 0.7113)	0.807
43y – 53y	0.5788 (-0.0199, 1.1776)	0.058	0.7507 (0.1235, 1.3778)	0.019
53y – 60/64y	-0.5310 (-1.1105, 0.0485)	0.072	-0.5197 (-1.1142, 0.0748)	0.087

SBP – Systolic blood pressure; BMI – body mass index; T2DM – type 2 diabetes mellitus; HTTT – hypertension treatment

Table 5.3g. Regression coefficients, 95% confidence intervals, and p values for a model showing effect of rate of change in SBP over 3 time periods (36-43y), (43-53y) and (53-60/64y) on s' at age 60-64y. Initial model adjusted for sex, age at clinic attendance and clinic attended. Final model also adjusted for BMI, T2DM and HTT.

Period of rate of change in SBP	Adjusted for sex, clinic attended and age		Also adjusted for BMI, T2DM and current HTT	
	β Coefficient (95%CI)	p value	β Coefficient (95%CI)	p value
36y – 43y	-0.014 (-0.116, 0.088)	0.793	0.015 (-0.090, 0.119)	0.784
43y – 53y	0.054 (-0.042, 0.150)	0.273	0.066 (-0.035, 0.167)	0.198
53y – 60/64y	-0.057 (-0.153, 0.039)	0.248	-0.084 (-0.181, 0.014)	0.093

SBP – Systolic blood pressure; BMI – body mass index; T2DM – type 2 diabetes mellitus; HTTT – hypertension treatment

Discussion

BP from early midlife predicted worse diastolic function at age 60-64y. This effect was independent of current BP; extended across the whole range of BP; and was not limited to people with hypertension, or those who went on to develop hypertension at the time when diastolic function was assessed. Further, we found that rapid rises in SBP between 43-53y and 53-60/64y were particularly influential in determining subsequent diastolic function. Since the rise in BP in the UK population typically begins to accelerate around the fourth decade of life until it slows again in later life,[18] we suggest that the period 40-60y may represent a sensitive period when rise in BP adversely influences future development of diastolic dysfunction. Finally, we found that HTT from early mid-life was associated with impaired diastolic function even when the effect of current BP was accounted for.

SBP and HTT were not consistently associated with EF. However, increased SBP at age 36y and HTT at 53y were associated with decreased s' (i.e. poorer systolic function). Rate of change in SBP was not consistently related to systolic function.

I will initially discuss the diastolic function findings and then the systolic function findings.

There has been limited work in the past on relating antecedent BP with future diastolic function. Arnlov et al reported that higher SBP and DBP at the age of 50y were associated with decreased E/A measured 20y later in the Swedish Uppsala cohort.[19] Hypertension is thought to cause diastolic dysfunction via impaired LV relaxation and reduced LV compliance.[20] Ultimately the elevated filling pressures associated with severe diastolic dysfunction can lead to HFPEF[21, 22] or pulmonary oedema.[23] Interestingly, Lee et al reported that higher BP and BMI in midlife were predictive of incident heart failure in later life in the

Framingham study.[9] Our data suggest that that this relationship may be mediated at least in part via increased diastolic dysfunction.

Effective management of diastolic dysfunction remains unclear as there have been few trials that have focused on this (as opposed to heart failure with decreased ejection fraction/systolic dysfunction) and the trials which have been done have demonstrated minimal benefit with conventional heart failure medication.[24, 25] This has led to the treatment of comorbidities/determinants of diastolic dysfunction (e.g. HTT) becoming a cornerstone of management of these patients.[26] Controlling BP is a class 1 recommendation from the American College of Cardiology and American Heart Association for the prevention of diastolic heart failure,[27] and large trials like ALLHAT and HYVET demonstrated the benefits of treating hypertension in terms of decreased incidence of new heart failure and heart failure admissions.[28, 29] In our cohort we found that from the age of 43y onwards, exposure to HTT was associated with worse diastolic function at age 60-64y (even if the BP had normalized with HTT). A possible explanation of this finding is that initiation of treatment was delayed too long to prevent irreversible damage at an earlier stage of life. If this is true, individuals at risk, for example, those with faster rises in BP, even within the so-called normal range, may need to be treated earlier. Another possible explanation is that although the BP was controlled when measured at the clinic visit, it remained poorly controlled at other times leading to worse diastolic function in these individuals on HTT.

Elevated BP is associated with LVH and this could contribute to impaired diastolic function. However, adjustment for LVMI had only modest effects on associations between antecedent BP and diastolic function and it seems that this relationship is largely independent of increased LVMI. Some cross-sectional studies have found PP to be the best predictor of

diastolic function,[30, 31] but we found relatively similar associations between antecedent SBP, DBP, PP and MAP and diastolic function.

E/e' had a more consistent relationship with BP and from an earlier age than some of the other measures of diastolic function. The reason for this may be that E/e' may be less load dependent and is likely to be more accurate across a range of severity of diastolic impairment.[32] E/A suffers from pseudonormalization as discussed below and in the methods chapter (chapter 3), and as such, the associations with previous BP may not be as strong. The other advantages of focussing on E/e' have been discussed in the methods chapter (chapter 3).

Few studies have related earlier BP or BP over time with later systolic function and the studies that have investigated this have demonstrated differing associations. Johnson et al showed that sustained higher SBP over a 5 year period among young adults (21-24y old at follow up), was associated with increased fractional shortening,[33] while Bjorklund et al showed that, over a 20y period (initial contact at age 50y), study members with sustained hypertension had the same follow-up EF as those with normal BP.[34] In our analyses, SBP was not associated with EF except at age 53y. However for SBP at age 53y, initial models were non-significant and it was only on adding SBP at 60-64y and on further adjustment that the effect size increased and significance was achieved. This may represent an artefact or it may imply that SBP at age 53y is associated with better systolic function (possibly an early compensatory response) when the effects of SBP, T2DM and BMI at age 60-64y are accounted for. If this is the case it would be difficult to explain why the effect is not seen before adjustment.

While the association of SBP at age 53y with EF was positive, that of SBP at 36y with s' was negative i.e. poorer systolic function. There was a marginal decrease in effect size through

sequential adjustments and it is interesting that only SBP at age 36y demonstrated this association. It is possible that increase in early BP causes a subtle decline in long axis function and it is important to note that s' does not measure the same aspect of systolic function that EF does. Long axis systolic function is closely linked to long axis diastolic function[35-40] and if systolic and diastolic function are 2 ends of the same continuum,[2, 3] a decrease in s' may reflect impending systolic dysfunction (as measured by an impending decrease in EF) in individuals with coexisting diastolic dysfunction. It is less clear why this association is not seen with the later SBP measures.

HTT at age 53y was associated with poorer systolic function in terms of decreased s'. It is possible that age 53y (and the period 43-53y; discussed below) may represent a sensitive period for systolic function. As mentioned previously, s' and EF are not analogous measures of systolic function, and as such, the differing effects of SBP and HTT at different times on EF and s' may represent differing responses of radial and longitudinal contractility to SBP.

Rate of change in SBP over the 43y-53y period was associated with an increase in EF in the fully adjusted model while the effect was just non-significant in the minimally adjusted model. It is possible that the effects of BMI, T2DM and HTT at age 60-64y need to be excluded before the effect of rate of change in SBP on EF is revealed. As seen with SBP at age 53y, the increase in EF may reflect and initial compensatory change due to increased afterload.

Strengths and limitations

General strengths and limitations relevant to this chapter have been previously discussed in the blood pressure-cardiac structure chapter (chapter 4).

We utilized tissue Doppler as our primary measure of diastolic function; this has the advantage that it can distinguish normal diastolic function from pseudonormalization.[41] Pseudonormalization will tend to attenuate relationships between antecedent BP and diastolic function assessed by E/A, and probably accounts for the generally weaker relationships seen using this measure of diastolic function.

Ideally we would have liked to interrogate further measures of systolic function (e.g. fractional shortening and wall stress relationships); however this was not possible due to the constraints of time.

Echocardiography was only carried out in the last round of data collection; hence the possibility of cardiac dysfunction preceding the rise in BP cannot be excluded.

Conclusions

BP from the age of 36y is associated with diastolic function in people aged 60-64y independently of current BP (E/e'); faster increases in BP in midlife are particularly detrimental. People on HTT have more adverse diastolic function even when current BP is taken into account suggesting that early risk factor modification may be important to prevent the adverse effects of BP on diastolic function. The associations between BP and systolic

function were less consistent although increased SBP at age 36y was associated with decreased s' at age 60-64y while HTT at age 53y was associated with decreased s'.

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Chapter 6

The relationship between adult life course body mass index and overweight and left ventricular mass

Introduction

The World Health Organization predicts that 2.3 billion adults will be overweight by the middle of this decade and that more than 700 million adults will be obese.[1] The trend to overweight is starting at younger ages now with 10% of school-age children estimated to be overweight with this figure rising to more than 30% for the Americas.[2]

Previously published work on the Medical Research Council National Survey of Health and Development (MRC NSHD) cohort has shown that median body weight and body mass index (BMI) rise over the life course (Figure 6.1) and the earlier an individual becomes overweight, the greater is their BMI in the future (Figure 6.2).[3]

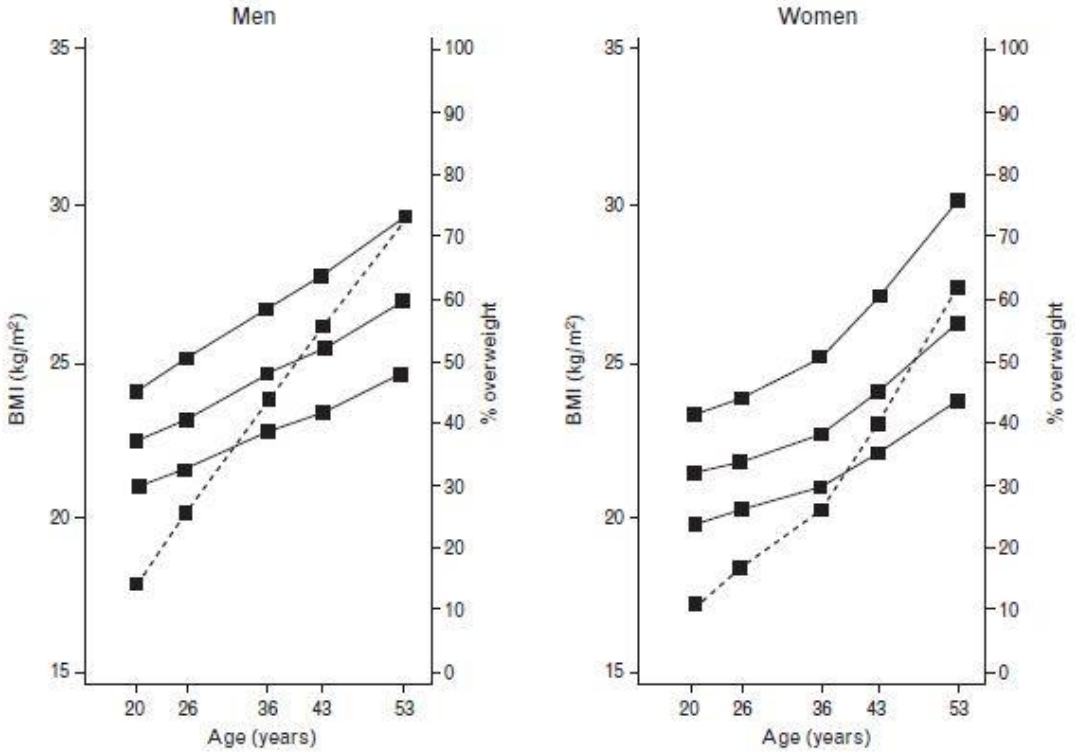


Figure 6.1. Median BMI and interquartile range (continuous line) and % of individuals overweight (BMI >25 Kg/m2) (broken line) in men and women at each age in adulthood.[3]

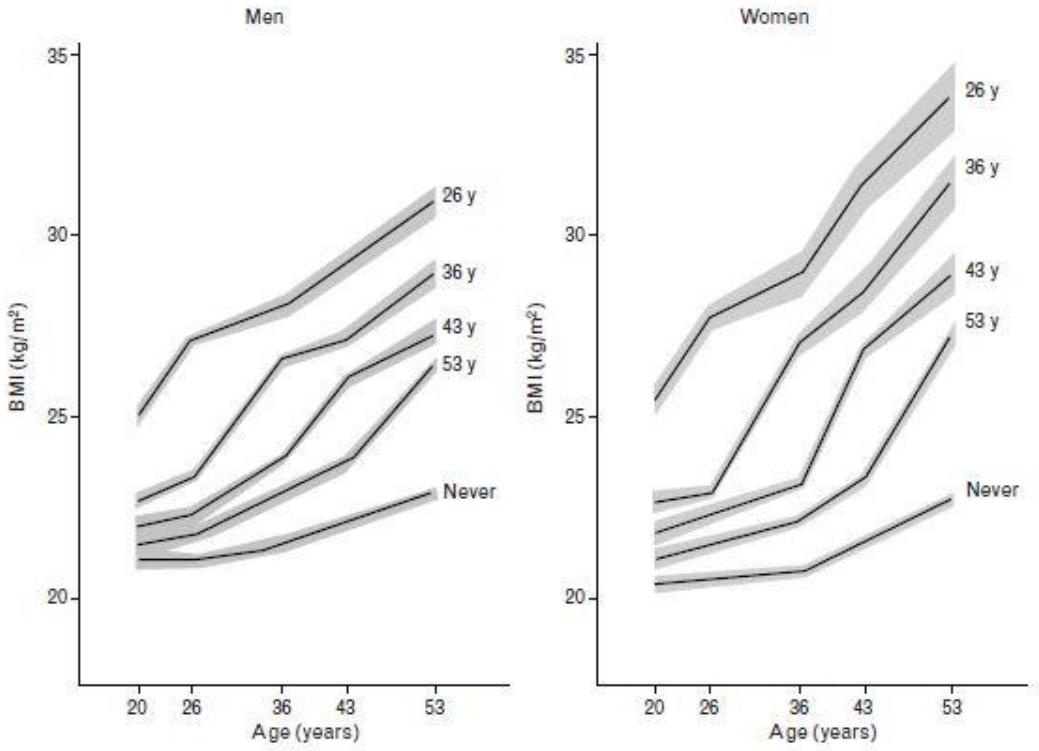


Figure 6.2. Observed mean BMI trajectories in men and women by age at which participant first became overweight. Shaded areas are 95% confidence intervals.[3]

A variety of changes to left ventricular (LV) structure occur with increased BMI and obesity.[4] Many cross-sectional studies in adults in their twenties to fifties have shown that obesity is independently associated with LV hypertrophy (LVH),[5-8] while others have shown increases in LV mass (LVM) correspond to increased BMI only if there are no associated comorbidities (e.g. hypertension, diabetes, coronary artery disease).[9-11] Earlier studies in the literature from the 1980s and 1990s, focussed on the relationship between cavity size and increased BMI and suggested LV dilation was associated with obesity.[12-14] However these studies were carried

out in small numbers of heart failure patients in whom the underlying aetiology of the heart failure itself may have played a greater role in determining LV cavity dimensions.[10, 11] More recent studies from the last decade, looking at larger cohorts of people of varying ages free from comorbidities, have demonstrated that overweight and obese individuals have a greater prevalence of LVH, increased LV cavity size and LV wall thickness compared to age-matched normal-weight controls.[10, 11, 15-17]

The effect of duration of overweight and obesity on cardiac structure has not been extensively explored in the literature. Alpert et al showed that increased duration of morbid obesity was associated with increased LVM indexed to height and with LV cavity size (duration of morbid obesity ranging from 5y to 28y)[13] but others have been unable to demonstrate an association between duration of obesity and cardiac structure.[17]

There is also evidence that obesity affects cardiac function. Obesity has been associated with diastolic dysfunction[18] and heart failure with preserved ejection fraction (HFpEF).[19] Increased LVM as a result of increased weight, leading to diastolic dysfunction, may be a putative mechanism of HFpEF in these patients.[20, 21] However, some studies have shown that the diastolic dysfunction associated with obesity is independent of LV geometry.[5] Data relating BMI and systolic function have shown inconsistent relationships.[17, 22] They are discussed more fully in the BMI-cardiac function chapter (chapter 7).

The aim of this chapter is to investigate the effect of adult BMI and prolonged overweight on cardiac structure as measured by echocardiography at age 60-64y based on longitudinal data derived from the MRC NHSD birth cohort.

Methods

The majority of relevant methods have been described previously in the methods chapter (chapter 3).

Statistical Analysis

Initially, separate regression models investigated the association between BMI at each of the 6 ages at which it was measured and LVM indexed to body surface area (BSA): LVMI-BSA with adjustment for sex, age at clinic visit and clinic attended. We tested whether these associations were linear and whether they were different for men and women. There was no gender interaction so in subsequent analyses both genders were pooled and adjusted for sex. Subsequent adjustments were made for systolic blood pressure (SBP) and type 2 diabetes mellitus (T2DM) at age 60-64y and then for BMI at age 60-64y. Similar analyses were also carried out replacing LVMI-BSA with LVM indexed to height raised to the power 2.7 – LVMI-$ht^{2.7}$ and with relative wall thickness (RWT).

In a similar series of models to those described above, BMI was replaced by overweight at each age. We then estimated the effect of age at first overweight [variable construction described in the methods chapter (chapter 3)] on cardiac structure. We tested for linearity across categories and then for deviation from linearity. Estimates from the categorical variable model and estimated marginal means are presented.

Results

General characteristics of the study population as relevant to this chapter are shown in Table 6.1. The correlation between mean BMI (combined for men and women) at the different ages is depicted in Table 6.2. A high degree of tracking is demonstrated with high correlations between BMI measured at adjacent ages with decreasing correlation with greater ages differences. Weaker correlations are seen with ages 20y and 26y. The increase in mean BMI with age is depicted in Figure 6.3.

Table 6.1. Echocardiographic and cardiac risk factor characteristics of study participants. Unless otherwise stated data refer to age 60-64y.

Variable (At age 60-64y unless stated otherwise)	Combined		Men		Women	
	n(%)	Mean (SD)	n(%)	Mean (SD)	n(%)	Mean (SD)
Age at echo (y)	1472	63.3 (1.1)	696	63.2 (1.1)	776	63.3 (1.1)
IVSD (cm)	1480	1.1 (0.2)	701	1.1 (0.2)	779	1.0 (0.2)
LVPWTD (cm)	1480	1.0 (0.2)	701	1.0 (0.2)	779	0.9 (0.2)
RWT	1480	0.4 (0.1)	701	0.4 (0.1)	779	0.4 (0.1)
LVM (g)	1480	181.3 (59.3)	701	209.2 (60.3)	779	156.1 (45.6)
LVMI-BSA (g/m^2)	1480	95.7 (26.6)	701	104.1 (27.9)	779	88.1 (22.9)
LVMI-$ht^{2.7}$ ($g/m^{2.7}$)	1480	44.2 (13.2)	701	46.1 (13.7)	779	42.4 (12.6)
BMI (Kg/m^2)	1480	27.5 (4.6)	701	27.7 (4.0)	779	27.4 (5.1)
Overweight (%)	1009 (68)		514 (73)		495 (64)	
Not overweight	465		185		280	
BMI at age 53y (Kg/m^2)	1411	26.8 (4.4)	660	27.0 (3.7)	751	26.8 (4.9)
Overweight at age 53y	891 (63)		456 (69)		435 (58)	
Not overweight at age 53y	517		202		315	
BMI at age 43y (Kg/m^2)	1400	24.9 (3.7)	664	25.2 (3.1)	736	24.6 (4.1)

Overweight at age 43y	592 (42)		337 (51)		255 (35)	
Not overweight at age 43y	794		323		471	
BMI at age 36y (Kg/m^2)	1341	23.6 (3.3)	631	24.3 (2.9)	710	23.0 (3.4)
Overweight at age 36y	384 (29)		238 (38)		146 (21)	
Not overweight at age 36y	924		384		540	
BMI at age 26y (Kg/m^2)	1307	22.5 (2.8)	616	23.0 (2.7)	691	22.0 (2.9)
Overweight at age 26y	199 (15)		122 (20)		77 (11)	
Not overweight at age 26y	1057		480		577	
BMI at age 20y (Kg/m^2)	1225	22.0 (2.6)	570	22.4 (2.3)	655	21.6 (2.8)
Overweight at age 20y	134 (11)		75 (13)		59 (9)	
Not overweight at age 20y	1021		484		537	
SBP (mm Hg)	1478	135.7 (17.9)	701	139.0 (17.7)	777	132.8 (17.7)
DBP (mm Hg)	1478	77.4 (9.7)	701	79.0 (9.8)	777	75.9 (9.3)
T2DM	1357		635		722	
Diabetic	73 (6)		37 (6)		36 (5)	

IVSD - Interventricular septal thickness in diastole; LVPWTD - Left ventricular posterior wall thickness in diastole; RWT - Relative wall thickness; LVM - Left ventricular mass; LVMI-BSA - Left ventricular mass indexed to body surface area; LVMI-ht$^{2.7}$ - Left ventricular mass indexed to height raised to the power 2.7; BMI - Body mass index; SBP - Systolic blood pressure; DBP - Diastolic blood pressure; T2DM - Type 2 diabetes mellitus

Table 6.2. Correlation between mean body mass indexes (combined for both sexes) at different ages.

	BMI at 60-64y	BMI at 53y	BMI at 43y	BMI at 36y	BMI at 26y	BMI at 20y
BMI at 60-64y	1.0000					
BMI at 53y	0.8607	1.0000				
BMI at 43y	0.7819	0.8530	1.0000			
BMI at 36y	0.7033	0.7680	0.8481	1.0000		
BMI at 26y	0.5475	0.6194	0.6924	0.7453	1.0000	
BMI at 20y	0.4461	0.5015	0.5727	0.6387	0.7781	1.0000

BMI – body mass index

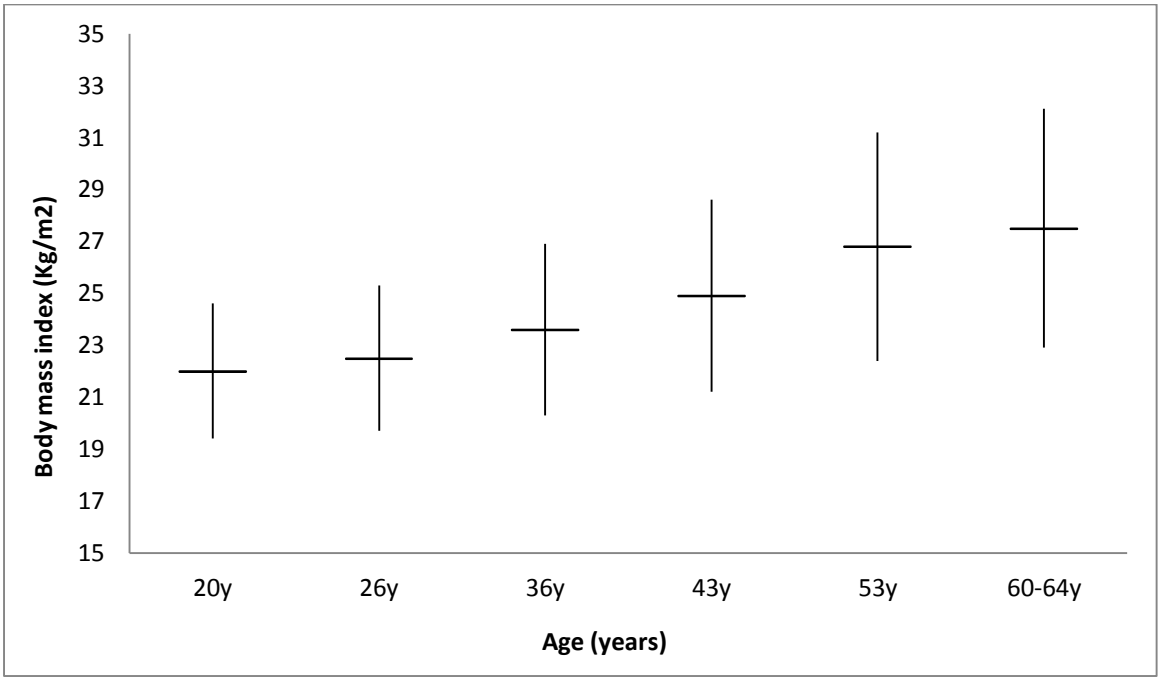


Figure 6.3. Combined mean Body mass index (BMI) for men and women (+/- 1 standard deviation) at different ages (20-60/64y) demonstrating a steady increase in mean BMI with increasing age.

The effect of BMI at different ages on LVMI-BSA, LVMI-$ht^{2.7}$ and RWT is presented in Tables 6.3a-c.

Increased BMI from the age of 20y onwards was associated with greater LVMI-BSA in a minimally adjusted model, and on inclusion of SBP and T2DM at age 60-64y, the estimates were generally only slightly attenuated (Table 6.3a). When BMI at age 60-64y was included in models, the effect of BMI at prior ages was reduced, although less so for ages 26y and 43y with the associations becoming non-significant for ages 20y and 36y.

Increased BMI from the age of 20y onwards was associated with greater LVMI-$ht^{2.7}$ in a minimally adjusted model and these relationships were only minimally attenuated following inclusion of the potential mediators, SBP and T2DM (at age 60-64y) (Table 6.3b). When BMI

at age 60-64y was included, effects of earlier BMI were reduced, but as for LVMI-BSA, BMI at 26y and 43y remained associated with LVMI- $ht^{2.7}$.

Higher BMI from age 43y onwards was associated with greater RWT (Table 6.3c); this remained the case when SBP and T2DM at age 60-64y were included in the model. A similar, although weaker, association was observed with BMI at age 26y which was attenuated after adjustment for SBP and T2DM. On including BMI at age 60-64y, the associations changed from positive to negative and also became non-significant except at age 36y.

Table 6.3a. Regression coefficients, 95% confidence intervals and p values estimating the effect of BMI at different ages on LVM indexed to body surface area at age 60-64y. Models adjusted for age, sex and clinic attended and then for systolic blood pressure and type 2 diabetes mellitus at age 60-64y and then for body mass index at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + BMI at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1133)	1.27 (0.71, 1.82)	<0.001	1.14 (0.58, 1.69)	<0.001	0.45 (-0.16, 1.07)	0.148
26 (n=1203)	1.77 (1.28, 2.27)	<0.001	1.58 (1.08, 2.08)	<0.001	0.92 (0.32, 1.52)	0.003
36 (n = 1236)	1.54 (1.11, 1.96)	<0.001	1.33 (0.90, 1.77)	<0.001	0.59 (-0.02, 1.20)	0.060
43 (n = 1289)	1.46 (1.10, 1.82)	<0.001	1.40 (0.93, 1.87)	<0.001	1.28 (0.90, 1.65)	<0.001
53 (n = 1282)	0.80 (0.20, 1.40)	0.009	1.04 (0.74, 1.35)	<0.001	0.64 (0.01, 1.28)	0.046
60-64 (n = 1353)	1.17 (0.89, 1.45)	<0.001	0.99 (0.70, 1.28)	<0.001	-	-

SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

Table 6.3b. Regression coefficients, 95% confidence intervals and p values estimating the effect of BMI at different ages on LVM indexed to $ht^{2.7}$ at age 60-64y. Models adjusted for age, sex and clinic attended and then for systolic blood pressure and type 2 diabetes mellitus at age 60-64y and then for body mass index at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + BMI at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1133)	1.17 (0.89, 1.45)	<0.001	1.08 (0.800, 1.36)	<0.001	0.21 (-0.08, 0.51)	0.152
26 (n=1203)	1.50 (1.25, 1.74)	<0.001	1.37 (1.12, 1.62)	<0.001	0.45 (0.16, 0.73)	0.002
36 (n = 1236)	1.42 (1.21, 1.63)	<0.001	1.30 (1.08, 1.51)	<0.001	0.24 (-0.05, 0.54)	0.100
43 (n = 1289)	1.37 (1.19, 1.54)	<0.001	1.27 (1.09, 1.45)	<0.001	0.38 (0.09, 0.66)	0.010
53 (n = 1304)	1.20 (1.06, 1.35)	<0.001	1.12 (0.97, 1.26)	<0.001	0.29 (-0.01, 0.59)	0.058
60-64 (n = 1353)	1.23 (1.10, 1.37)	<0.001	1.14 (1.00, 1.28)	<0.001	-	-

SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

Table 6.3c. Regression coefficients, 95% confidence intervals and p values estimating the effect of BMI at different ages on relative wall thickness at age 60-64y. Models adjusted for age, sex and clinic attended and then for systolic blood pressure and type 2 diabetes mellitus at age 60-64y and then for body mass index at age 60-64y

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + BMI at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1131)	0.00082 (-0.00110, 0.00274)	0.403	0.00071 (-0.00123, 0.00265)	0.473	-0.00121 (-0.00337, 0.00096)	0.275
26 (n=1201)	0.00174 (-0.00002, 0.00348)	0.050	0.00140 (-0.00037, 0.00317)	0.121	-0.00065 (-0.00278, 0.00149)	0.552
36 (n = 1234)	0.00087 (-0.00061, 0.00236)	0.248	0.00052 (-0.00100, 0.00205)	0.502	-0.00285 (-0.00500, -0.00071)	0.009
43 (n = 1287)	0.00183 (0.00057, 0.00310)	0.005	0.00152 (0.00021, 0.00284)	0.023	-0.00131 (-0.00343, 0.00081)	0.227
53 (n = 1302)	0.00216 (0.00110, 0.00322)	<0.001	0.00190 (0.00080, 0.00300)	0.001	-0.00003 (-0.00231, 0.00225)	0.980
60-64 (n = 1351)	0.00244 (0.00144, 0.00343)	<0.001	0.00209 (0.00106, 0.00312)	<0.001	-	-

SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus; BMI - Body mass index

The effect of being overweight (BMI >=25 kg/m^2) at different ages on future LVMI-BSA, LVMI-$ht^{2.7}$ and RWT is presented in Tables 6.4a-c.

Overweight from the age of 20y onwards was predictive of increased LVMI-BSA in a minimally adjusted model with the effect size weakest at 20y and strongest at 60-64y (Table 6.4a). When SBP and T2DM at age 60-64y were included, the effect of overweight was slightly reduced with overweight at age 20y becoming non-significant. When overweight at 60-64y was included in the model, coefficients were generally halved but remained positive and overweight at age 26y and 43y were independently associated with increased LVMI-BSA.

The overall pattern of association between overweight and LVMI- $ht^{2.7}$ was qualitatively similar to that between overweight and LVMI-BSA (Table 6.4b). Overweight from the age of 20y onwards was associated with greater LVMI-$ht^{2.7}$ in all the models and at all ages. There was a slight reduction in effect size with successive adjustment for SBP and T2DM at 60-64y and then for overweight at 60-64y.

Increased RWT was seen with overweight from age 43y onwards and was strongest at age 60-64y in a minimally adjusted model and on inclusion of SBP and T2DM at age 60-64y (Table 6.4c). When overweight at 60-64y was included in the model, the associations were almost completely explained.

Table 6.4a. Regression coefficients (g/m^2), 95% confidence intervals and p values estimating the effect of being overweight at different ages on LVM indexed to body surface area at age 60-64y. Models adjusted for age, sex and clinic attended and then for systolic blood pressure and type 2 diabetes mellitus at age 60-64y and then for being overweight at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 +SBP and T2DM at 60-64y)		Model 3 (Model 2 + overweight at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1070)	5.12 (0.54, 9.70)	0.028	4.12 (-0.43, 8.67)	0.076	1.94 (-2.63, 6.51)	0.404
26 (n=1156)	9.93 (5.98, 13.88)	0.001	8.40 (4.43, 12.37)	<0.001	5.55 (1.52, 9.58)	0.007
36 (n = 1204)	6.67 (3.47, 9.87)	<0.001	5.38 (2.16, 8.60)	0.001	2.33 (-1.05, 5.70)	0.176
43 (n = 1276)	8.14 (5.34, 10.94)	<0.001	6.79 (3.95, 9.62)	<0.001	3.71 (0.58, 6.85)	0.020
53 (n = 1302)	8.94 (6.17, 11.70)	<0.001	7.54 (4.76, 10.32)	<0.001	3.22 (-0.31, 6.75)	0.074
60-64 (n = 1349)	10.99 (8.15, 13.83)	<0.001	9.42 (6.52, 12.31)	<0.001	-	-

SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus

Table 6.4b. Regression coefficients (g/m$^{2.7}$), 95% confidence intervals and p values estimating the effect of being overweight at different ages on LVM indexed to ht$^{2.7}$ at age 60-64y. Models adjusted for age, sex and clinic attended and then for systolic blood pressure and type 2 diabetes mellitus at age 60-64y and then for being overweight at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 +SBP and T2DM at 60-64y)		Model 3 (Model 2 + overweight at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1070)	6.10 (3.74, 8.46)	<0.001	5.42 (3.11, 7.74)	<0.001	3.31 (1.06, 5.57)	0.004
26 (n=1156)	8.74 (6.74, 10.75)	<0.001	7.76 (5.77, 9.76)	<0.001	5.23 (3.26, 7.19)	<0.001
36 (n = 1204)	7.01 (5.39, 8.63)	<0.001	6.23 (4.61, 7.85)	<0.001	3.54 (1.89, 5.19)	<0.001
43 (n = 1276)	7.83 (6.43, 9.23)	<0.001	6.995 (5.585, 8.405)	<0.001	4.16 (2.63, 5.70)	<0.001
53 (n = 1302)	8.25 (6.86, 9.63)	<0.001	7.41 (6.03, 8.80)	<0.001	3.45 (1.71, 5.18)	<0.001
60-64 (n = 1349)	9.83 (8.43, 11.24)	<0.001	8.92 (7.50, 10.34)	<0.001	-	-

SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus

Table 6.4c. Regression coefficients, 95% confidence intervals and p values estimating the effect of being overweight at different ages on relative wall thickness at age 60-64y. Models adjusted for age, sex and clinic attended and then for systolic blood pressure and type 2 diabetes mellitus at age 60-64y and then for being overweight at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 +SBP and T2DM at 60-64y)		Model 3 (Model 2 + overweight at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1068)	0.0068 (-0.0092, 0.0227)	0.405	0.0057(-0.0102, 0.0217)	0.481	0.0008 (-0.0153, 0.0169)	0.923
26 (n=1154)	0.0059 (-0.0079, 0.1973)	0.402	0.0036 (-0.0104, 0.0175)	0.681	-0.0020 (-0.0163, 0.0123)	0.784
36 (n = 1202)	0.0067 (-0.0044, 0.0177)	0.237	0.0047 (-0.0065, 0.0158)	0.415	-0.00054 (-0.0124, 0.0113)	0.929
43 (n = 1274)	0.0129 (0.0031, 0.0227)	0.010	0.0105 (0.00052, 0.02042)	0.039	0.0042 (-0.0069, 0.0152)	0.458
53 (n = 1300)	0.0135 (0.0037, 0.0233)	0.007	0.0104 (0.00044, 0.02034)	0.041	0.00059 (-0.0121, 0.0132)	0.927
60-64 (n = 1347)	0.0230 (0.0130, 0.0330)	<0.001	0.0190 (0.0088, 0.0292)	<0.001	-	-

SBP - Systolic blood pressure; T2DM - Type 2 diabetes mellitus

The effect of age at first overweight on future LVMI-BSA, LVMI-$ht^{2.7}$ and RWT is presented in Tables 6.5a-c and Figures 6.4a-c.

There was an overall significant linear trend of increase in LVMI-BSA with earlier age at first overweight with the greatest effect in those overweight at 26y (Table 6.5a, Figure 6.4a). The trend seemed to start at age 26y with some levelling off at ages 20y and 36y. The test for deviation from a linear trend was borderline significant (p= 0.0492). The trend was maintained when SBP and T2DM at age 60-64y were included in the model. When BMI at age 60-64y was included in the model, the coefficients were reduced by varying extents at the different ages at first overweight, with the effect at some of the ages becoming non-significant and with the overall linear trend also becoming non-significant.

The relationship between age at first overweight and LVMI-$ht^{2.7}$ (Table 6.5b, Figure 6.4b) was qualitatively similar to that between age at first overweight and LVMI-BSA where the trend of increasing LVMI- $ht^{2.7}$ with earlier age at first overweight levelled off at the younger ages. The test for deviation from linear trend was significant (p = 0.0013). When BMI at age 60-64y was included in the final model, nearly all the coefficients for different ages at first overweight became non-significant while the overall test for linear trend was also non-significant.

In a minimally adjusted model, there was an overall weaker linear trend of increase in RWT with earlier age at first overweight (Table 6.5c, Figure 6.4c). The coefficient at age 26y was non-significant and the coefficients for age 36y and later were similar in magnitude. The test for deviation from linear trend was non-significant (p = 0.1327). In contrast to LVMI, the trend for linearity became non-significant on the addition of SBP and T2DM at age 60-64y to the model, as the effects were slightly attenuated. When BMI at age 60-64y was included in

the model, the effects were attenuated with reversal of association at earlier ages (the coefficients became negative for ages 20y to 36y although they were non-significant).

Table 6.5a. Regression coefficients (g/m^2), 95% confidence intervals and p values estimating the effect of age at first overweight on LVM indexed to body surface area at 60-64 years in men and women.

Age at first diagnosis of overweight (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP at 60-64y + T2DM)		Model 3 (Model 2 + BMI at 60-64y)	
	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend
20	15.18 (8.04, 22.32)	<0.001	12.42 (5.18, 19.66)	<0.001	5.76 (-4.85, 16.37)	0.222
26	20.64 (12.54, 28.75)		16.76 (8.46, 25.06)		10.78 (-0.06, 21.61)	
36	13.05 (6.87, 19.22)		11.03 (4.76, 17.30)		6.33 (-1.99, 14.65)	
43	14.43 (8.42, 20.44)		12.18 (6.06, 18.30)		8.73 (1.41, 16.05)	
53	10.16 (4.78, 15.55)		8.71 (3.25, 14.17)		6.10 (-0.14, 12.34)	
60-64	6.57 (-0.51, 13.66)		5.59 (-1.49, 12.68)		3.65 (-3.78, 11.08)	

SBP - Systolic blood pressure; T2DM - Type 2 Diabetes mellitus; BMI - Body mass index

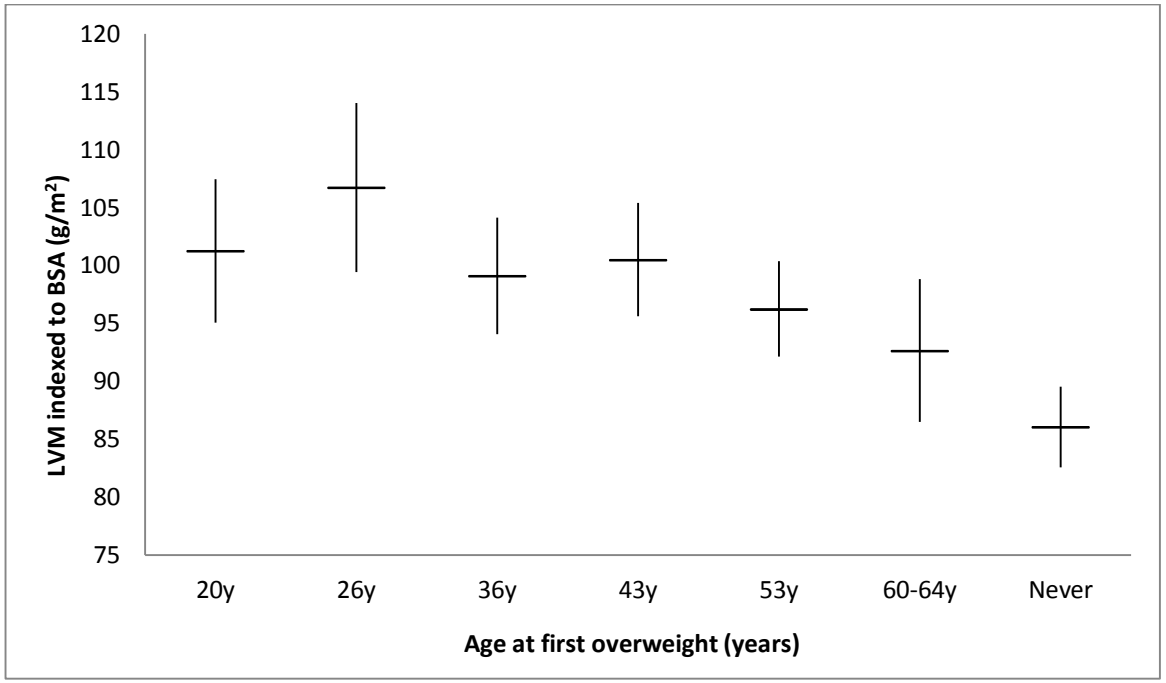


Figure 6.4a. Estimated marginal means in men and women of left ventricular mass indexed to body surface area (g/m^2) for different ages at first overweight and for never overweight for model 1 (above).

Table 6.5b. Regression coefficients (g/m$^{2.7}$), 95% confidence intervals and p values estimating the effect of age at first overweight on LVM indexed to ht$^{2.7}$ at 60-64 years in men and women.

Age at first diagnosis of overweight (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP at 60-64y + T2DM)		Model 3 (Model 2 + BMI at 60-64y)	
	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend
20	15.36 (11.85, 18.87)	<0.001	13.81 (10.26, 17.36)	<0.001	2.59 (-2.50, 7.67)	0.248
26	17.29 (13.30, 21.28)		15.14 (11.07, 19.21)		5.06 (-0.14, 10.25)	
36	12.03 (8.99, 15.07)		10.96 (7.88, 14.03)		3.04 (-0.95, 7.03)	
43	11.35 (8.40, 14.32)		10.20 (7.20, 13.21)		4.39 (0.89, 7.90)	
53	8.12 (5.47, 10.77)		7.37 (4.70, 10.05)		2.99 (-0.01, 5.98)	
60-64	5.53 (2.05, 9.02)		5.08 (1.60, 8.55)		1.80 (-1.77, 5.36)	

SBP - Systolic blood pressure; T2DM - Type 2 Diabetes mellitus; BMI - Body mass index

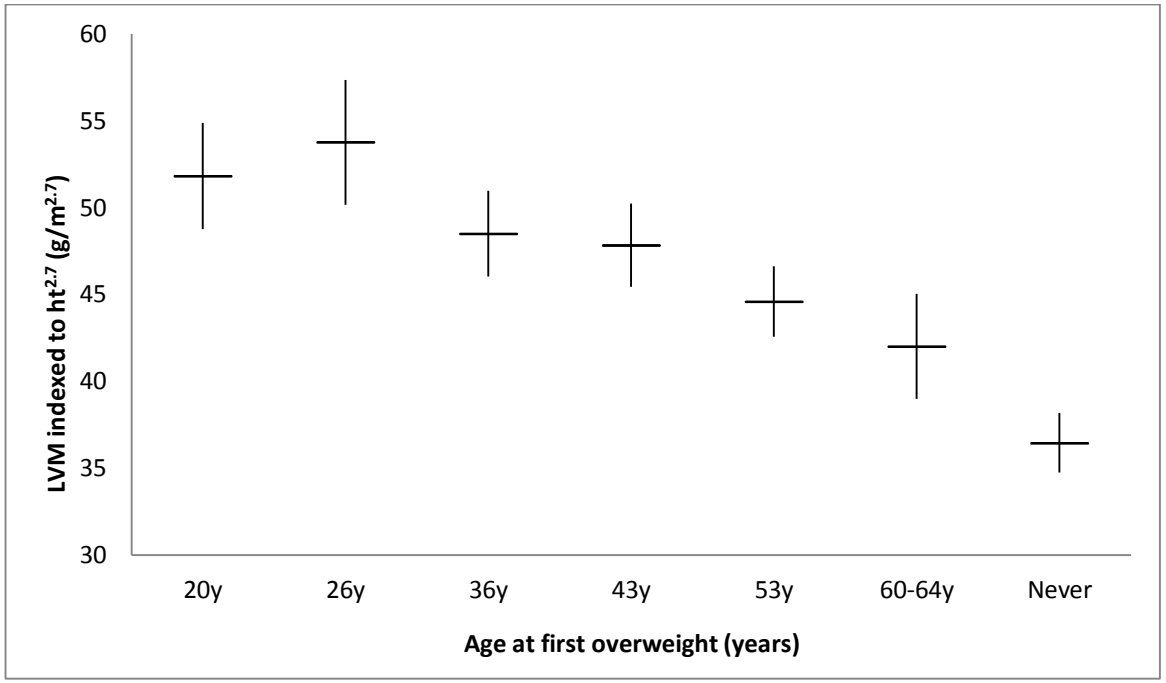


Figure 6.4b. Estimated marginal means in men and women of left ventricular mass indexed to $ht^{2.7}$ ($g/m^{2.7}$) for different ages at first overweight and for never overweight for model 1 (above).

Table 6.5c. Regression coefficients, 95% confidence intervals and p values estimating the effect age at first overweight on relative wall thickness at 60-64 years in men and women.

Age at first diagnosis of overweight (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP at 60-64y + T2DM)		Model 3 (Model 2 + BMI at 60-64y)	
	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend
20	0.031 (0.0061, 0.0560)	0.037	0.024 (-0.0008, 0.0498)	0.187	-0.0106 (-0.0476, 0.0264)	0.136
26	0.012 (-0.017, 0.040)		0.0021 (-0.069, 0.0311)		-0.0295 (-0.0673, 0.0083)	
36	0.025 (0.0038, 0.0471)		0.020 (-0.0025, 0.04150		-0.0052 (-0.0342, 0.0238)	
43	0.028 (0.0070, 0.0491)		0.020 (-0.0011, 0.0417)		0.0022 (-0.0234, 0.0258)	
53	0.025 (0.0058, 0.0435)		0.018 (-0.0014, 0.0369)		0.0039 (-0.0179, 0.0258)	
60-64	0.027 (0.0022, 0.0518)		0.023 (-0.0022, 0.0473)		0.0122 (-0.0137, 0.0381)	

SBP - Systolic blood pressure; T2DM - Type 2 Diabetes mellitus; BMI - Body mass index

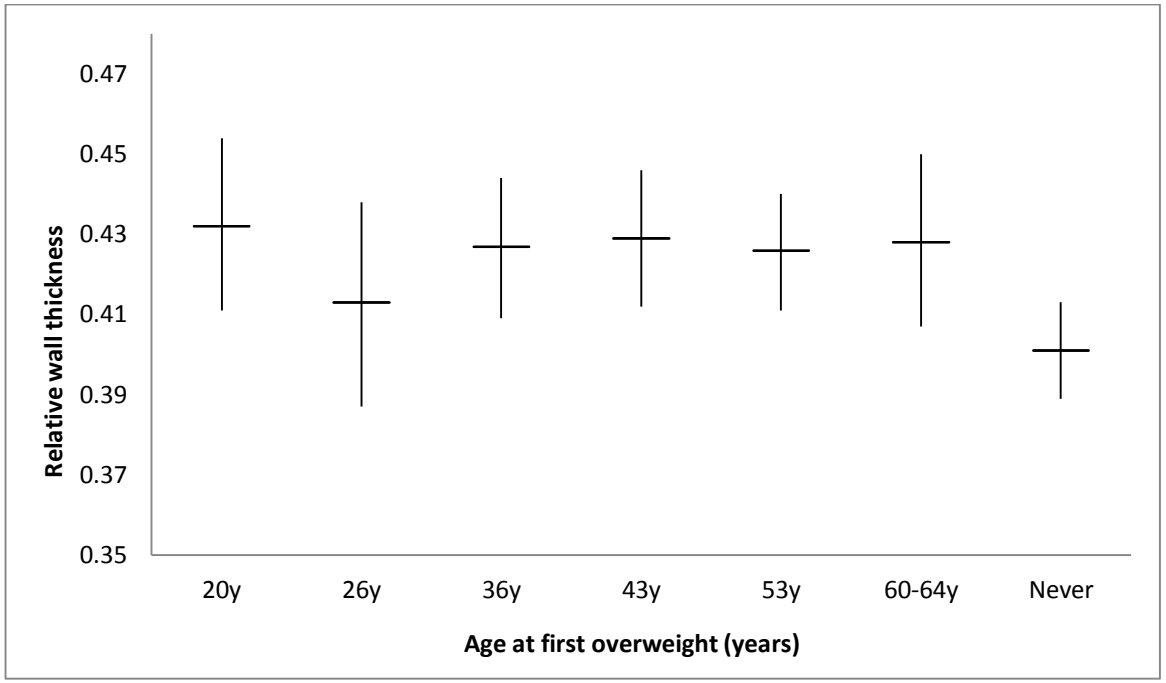


Figure 6.4c. Estimated marginal means in men and women of relative wall thickness for different ages at first overweight and for never overweight for model 1 (above).

Discussion

We found that increased BMI from the age of 20y onwards was associated with increased LVMI-BSA/LVMI-ht$^{2.7}$ in minimally adjusted models and after adjustment for SBP and T2DM. There was some evidence that the effect of prior BMI on LVMI remained even after adjustment for BMI at age 60-64y, with the effects at ages 26y and 43y being significantly independently associated with increased LVMI. This pattern of persistent adverse effect of prior overweight was replicated when BMI at different ages was replaced with overweight at different ages. Earlier age at first overweight was associated with greater LVMI in a minimally adjusted model and when SBP and T2DM at age 60-64y were included.

BMI and overweight appeared to be less strongly associated with RWT. Positive associations were present only from age 43y onwards in minimally adjusted models and when SBP and T2DM at age 60-64y were included. In a minimally adjusted model, earlier age at first overweight was associated with greater RWT.

Demonstrating an association between earlier adult BMI and overweight and later cardiac structure is an important step forward in understanding the effect prolonged exposure to overweight and elevated BMI have on the heart. While research has shown that earlier overweight can lead to long-lasting detrimental effects on cardiac function, there is far less work relating longitudinal measures of BMI to future cardiac structure.[4, 12, 13]

Current BMI (BMI at age 60-64y) did not explain the total effect of prior BMI, and in particular BMI at ages 26y to 43y remained associated with LVMI-BSA. It is possible that these ages represent a sensitive period for weight gain, the effect of which on cardiac structure is not entirely due to *tracking* (earlier increased BMI associated with later increased BMI). When we

consider the effect of overweight we see that there may be additional evidence for a sensitive period as overweight at ages 26y and 43y is associated with increased LVMI-BSA even when current overweight (overweight at 60-64y) is accounted for. If we put this in the context of the overall results, the interpretation may rather be that BMI/overweight from age 26y onwards has an effect over and above BMI/overweight at age 60-64y. It is also worth noting in this context, that this is the same time period that there is accelerated weight gain in our cohort (especially for women) (Figure 6.1).

It is difficult to disentangle the role of tracking of BMI from persistent exposure in these analyses. When the age at first overweight analyses are examined, we see that on inclusion of BMI at 60-64y, the linear trend for earlier age of first overweight being associated with increased LVMI becomes non-significant. The test for deviation from linear trend is significant for both LVMI outcomes (LVMI-BSA and LVM-$ht^{2.7}$) indicating that a non-linear trend may be present. This may reflect that high BMI/overweight at younger ages is due to higher muscle mass, while increased BMI/overweight at older ages represents fat mass.

The loss of significance when BMI at age 60-64y was included in the models may indicate that there is sufficient tracking of BMI for BMI at 60-64y to encompass the effect of previous BMI history (Table 6.2). However, it is important to note that this was not always the case. Due to the presence of BMI tracking, it is impossible to clearly differentiate whether length of overweight is more important than overweight at 60-64y.

From a preventive Cardiology viewpoint preventing overweight at an early stage should be warranted based on our findings especially since it is easier to stop people becoming

overweight or to reduce small amount of weight rather than to lose large amounts of weight when obese.[23]

Our analyses showed similar associations for both LVMI outcomes. In the setting of significant obesity, LVMI-BSA can be lower than normal as BSA increases more than LV weight.[8, 24, 25] Allometric indexation is felt by some to be the optimal correction factor as it minimizes gender differences in cardiac geometry.[26] In this context it is interesting that there were no major differences in our results when using LVMI-BSA and LVMI-$ht^{2.7}$ except for the fully-adjusted overweight-LVMI models where the associations with LVMI- $ht^{2.7}$ were more consistent on inclusion of overweight at 60-64y. This may be due to falsely-low LVMI-BSA due to greater increases in BSA in these overweight individuals as discussed above.

Overall however, it is possible that while the majority of our cohort are overweight at 60-64y, there may not be enough obesity [n = 286 (19%)] or morbid obesity [n = 98 (7%)] to skew all the LVMI-BSA results.

Compared to the associations with LVMI, associations of BMI and overweight with RWT were manifest at only older ages. Given the weaker strength of the associations, overweight at 60-64y may be more influential than age at first overweight. It is also possible that increased BMI affects RWT through a mechanism of "accumulated insult" i.e. only sustained elevated BMI over a period of time can affect RWT.

When BMI at 60-64y is included in the model, there is a reversal of the association, which may support BMI at 60-64y being more important than previous BMI history. However the reversal of effect is only significant at age 36y and the overall linear trend is non-significant. This may

reflect that while tracking of BMI occurs, it is possible that elevated BMI at 36y is independently reflective of earlier increased BMI and it is this accumulated increased BMI that is associated with changes in RWT. Alternatively it could be artefact or it could imply that greater increase in BMI is associated with a greater propensity to eccentric remodelling or LV chamber dilation.

In contrast to LVMI, the linear trend of earlier age at first overweight being associated with increased RWT, became non-significant when SBP and T2DM at age 60-64y were included in the model. This may imply that LV geometry (LVG) i.e. RWT is affected differently by increased BMI than is LVMI. SBP and T2DM may capture the effect of changes in BMI on RWT. An alternative explanation may be that increased BMI causes increased SBP or incidence of T2DM and these secondary increases lead to increased RWT. A third possibility is that, the association may have become non-significant after inclusion of SBP and T2DM, due to a weaker initial association with RWT (compared to LVMI) rather than due to substantial confounding. We should also remember that only SBP at age 60-64y has been included in the model and not SBP history. It is also worth noting that the linear trend for RWT in the minimally adjusted model (model 1) is weaker than the corresponding linear trends for both LVMI outcomes. This may imply that there is less evidence of a cumulative effect of overweight on RWT.

Strengths and limitations

Generalization to the UK population and the issue of missing data have been discussed in previous chapters.

The heights and weights recorded at ages 20 and 26y were self-reported. Although collected at the respective ages (and thus not subject to recall bias) they were not measured by trained staff in a controlled environment unlike at the other years, this may have introduced some reporting bias if people have a tendency to under-report their weight or over-estimate their height.[27] However, the former bias may be less problematic at 20y and 26y as most study members had normal BMIs at those ages.

The imbalance between energy intake and expenditure is an important factor in weight gain and the development of obesity as is total energy intake.[28-30] While some have shown that exercise and physical activity is associated with maintenance of a normal body weight,[31, 32] this area is more controversial with some studies not demonstrating such a relationship.[33, 34] In our cohort diet diaries and a questionnaire relating to physical activity have been collected, while objective measurements of physical activity were captured using Actiheart devices (CamNtech Ltd, Cambridge, UK). These data could not be incorporated in this work as they were unavailable at the time of analysis.

While body composition data had been collected in the last round of data collection this was not available at the time of my analyses and as such could not be incorporated. The addition of such data would have better elucidated the role of fat distribution in the body, possibly highlighting any gender differences.

Echocardiography was only carried out in the last round of data collection. As such, with no baseline echocardiography, the possibility of increased LVMI or RWT being a pre-existing diagnosis cannot be excluded. Reverse causality (prior cardiac structural abnormalities leading directly or indirectly to decreased exercise capacity and increased BMI and overweight in the future) also cannot be excluded.

Conclusions

Higher BMI and overweight from the age of 20y onwards is associated with increased LVMI when aged 60-64y. The earlier the diagnosis of overweight, the greater the increase in LVMI/RWT at age 60-64y. Current BMI/overweight captures some of the effects of previous BMI/overweight history on future LVM and RWT. These finding indicate that earlier weight reduction and achieving optimal BMI levels may prevent a future increase in LVM.

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Chapter 7

The relationship between adult life course BMI, overweight and age at first diagnosis of overweight and future cardiac function

Introduction

The prevalence of overweight individuals and obesity is rising with 300 million adults diagnosed with obesity at the turn of the 21st century.[1, 2] Increased body mass index (BMI) is associated with increased risk of congestive heart failure.[3] A variety of mechanisms have been proposed to link adiposity to cardiac dysfunction, including chronically increased workload,[4] direct lipotoxic[5] or adverse metabolic effects on cardiomyocyte function,[6] indirect effects via hypertension, dyslipidaemia, diabetes or chronic inflammation[4, 7] or effects on right ventricular function, including those due to the consequences of sleep apnoea.[4] There is also evidence that increased obesity is associated with diastolic dysfunction[8] and heart failure with preserved ejection fraction (HFPEF).[9] Nevertheless, there is still considerable uncertainty

regarding the effects of adiposity on cardiac function in the absence of heart failure and there is no firm pathological evidence of an obesity-induced cardiomyopathy.[12] Some studies have shown that estimates of systolic function [ejection fraction (EF), midwall fractional shortening] are either unchanged in obese individuals[10] or show a hyperdynamic pattern.[11] The adverse effect of obesity on diastolic function, may be mediated through an alteration in left ventricular (LV) filling indices secondary to an increase in LV mass (LVM).[12, 13] However, some studies have also shown that the diastolic dysfunction associated with obesity is independent of LV geometry.[14] The effect of the duration of obesity on diastolic function is even more controversial. Early work from the mid-1980s to mid-1990s seemed to show a relationship between increased duration of obesity and diastolic dysfunction, [15-17] but later studies from the middle of the last decade onwards do not bear out this association.[18, 19] All these studies have been limited by small sample sizes and duration of obesity was subject to recall bias.

The aim of this chapter is to investigate the effect of adult BMI and prolonged overweight on cardiac function as measured by echocardiography at age 60-64y based on longitudinal data derived from the NHSD birth cohort.

Methods

The majority of relevant methods have been described previously in the methods chapter (chapter 3).

Statistical Analysis

Initially, separate regression models investigated the association between BMI at each of the 6 ages at which it was measured and measures of cardiac function [E/e', E/A, e', e'/a', left atrial volume indexed to body surface area (LAVI), ejection fraction (EF) and s' (measures having been defined in the methods chapter – chapter 3)]. Adjustments were initially made for sex, age at clinic visit and clinic attended. Subsequent adjustments were made for systolic blood pressure (SBP) and presence of type 2 diabetes mellitus (T2DM) at age 60-64y and then for left ventricular mass indexed to body surface area (LVMI). The final model also included BMI at age 60-64y. We tested whether these associations were linear and whether they were different for men and women. There was no gender interaction so in subsequent analyses both genders were pooled and adjusted for sex.

In similar models to those above, BMI was replaced by overweight at each age and then by age at first overweight (variable derivation described in detail in methods chapter). Serial adjustments as described above were made with the final model in the series looking at the effect of overweight at the different ages also including overweight at age 60-64y (instead of BMI at age 60-64y).

Results

General characteristics of the study population relevant to his chapter are shown in Table 7.1. The pattern of increase in mean BMI over time and tracking have been graphically depicted/tabulated in the chapter on BMI-cardiac structure (chapter 6).

Table 7.1. Echocardiographic and cardiac risk factor characteristics of study participants.

Unless otherwise stated data refer to age 60-64y.

Variable (At age 60-64y unless stated otherwise)	Combined		Men		Women	
	n(%)	Mean (SD)	n(%)	Mean (SD)	n(%)	Mean (SD)
Age at echo (y)	1472	63.3 (1.1)	696	63.2 (1.1)	776	63.3 (1.1)
E/A	1424	1.0 (0.3)	668	1.0 (0.3)	756	1.0 (0.3)
e’	1381	8.8 (1.9)	640	8.9 (1.9)	741	8.7 (1.9)
E/e’	1354	8.0 (2.1)	681	7.5 (2.1)	727	8.3 (2.1)
e’/a’	1358	0.8 (0.2)	624	0.8 (0.2)	734	0.9 (0.2)
LAVI (ml/m^2)	1285	20.9 (7.3)	624	21.7 (7.5)	661	20.0 (7.0)
Ejection Fraction (%)	1453	68.7 (9.7)	687	67.2 (10.1)	766	69.9 (9.2)
s’ (cm/sec)	1350	7.7 (1.6)	626	8.1 (1.7)	724	7.5 (1.4)
BMI (Kg/m^2)	1480	27.5 (4.6)	701	27.7 (4.0)	779	27.4 (5.1)
Overweight	1009 (68)		514 (73)		495 (64)	
Not overweight	465		185		280	
BMI at age 53y (Kg/m^2)	1411	26.8 (4.4)	660	27.0 (3.7)	751	26.8 (4.9)
Overweight at age 53y	891 (63)		456 (69)		435 (58)	

Not overweight at age 53y	517		202		315	
BMI at age 43y (Kg/m^2)	1400	24.9 (3.7)	664	25.2 (3.1)	736	24.6 (4.1)
Overweight at age 43y	592 (42)		337 (51)		255 (35)	
Not overweight at age 43y	794		323		471	
BMI at age 36y (Kg/m^2)	1341	23.6 (3.3)	631	24.3 (2.9)	710	23.0 (3.4)
Overweight at age 36y	384 (29)		238 (38)		146 (21)	
Not overweight at age 36y	924		384		540	
BMI at age 26y (Kg/m^2)	1307	22.5 (2.8)	616	23.0 (2.7)	691	22.0 (2.9)
Overweight at age 26y	199 (15)		122 (20)		77 (11)	
Not overweight at age 26y	1057		480		577	
BMI at age 20y (Kg/m^2)	1225	22.0 (2.6)	570	22.4 (2.3)	655	21.6 (2.8)
Overweight at age 20y	134 (11)		75 (13)		59 (9)	
Not overweight at age 20y	1021		484		537	
SBP (mm Hg)	1478	135.7 (17.9)	701	139.0 (17.7)	777	132.8 (17.7)
DBP (mm Hg)	1478	77.4 (9.7)	701	79.0 (9.8)	777	75.9 (9.3)
T2DM	1357		635		722	
Diabetic	73 (6)		37 (6)		36 (5)	

LAVI - Left atrial volume indexed to body surface area; BMI - Body mass index; SBP - Systolic blood pressure; DBP - Diastolic blood pressure; T2DM - Type 2 diabetes mellitus

The effect of BMI at different ages on diastolic function is presented in Tables 7.2a-e.

In a minimally adjusted model, increased BMI from the age of 26y was associated with increased E/e' i.e. worse diastolic function (Table 7.2a). When SBP and T2DM at age 60-64y were included there was marginal attenuation of the effect and the association held from age 26y onwards. The association remained from 36y onwards when LVMI was included in the model, and in addition, the regression coefficient for age 20y became negative. When BMI at 60-64y was included in the final model, the coefficients also became negative at ages 26y and 53y with increasing BMI at age 20y associated with significantly decreased E/e' i.e. better diastolic function.

In a minimally adjusted model, increased BMI from 20y was associated with decreased E/A i.e. worse diastolic function (Table 7.2b). This was also the case on adjusting for SBP and T2DM at age 60-64y and LVMI. The effect sizes did not change much with these sequential adjustments. On adding in BMI at 60-64y, the β coefficients from 26y onwards became positive, although all were small and none was significant.

When the association between BMI at different ages and e' was examined, a negative association was seen from age 36y onwards in the minimally adjusted model (i.e. increased BMI associated with worse diastolic function) (Table 7.2c). This was also the case on adjustment for SBP and T2DM at age 60-64y and LVMI with a marginal attenuation of the effect sizes. On including BMI at age 60-64, the associations became positive (i.e. better diastolic function) but none was significant.

The associations between BMI at different ages and e'/a' (Table 7.2d) were somewhat qualitatively similar to those between BMI and E/e'. In a minimally adjusted model, increased BMI from age 26y onwards was associated with decreased e'/a' i.e. worse diastolic function. This was the case from age 36y onwards on addition of SBP and T2DM at age 60-64y and when LVMI was included in the model. There was a small decrease in effect sizes on these sequential adjustments. When BMI at age 60-64y was included, the coefficients became positive (i.e. better diastolic function) and were significant at ages 20y and 26y.

The effect of BMI at different ages on LAVI was also examined (Table 7.2e) with increased BMI from the age of 20y onwards associated with greater LAVI in a minimally adjusted model and on inclusion of SBP and T2DM at age 60-64y. This was the case from age 26y onwards when LVMI was also included in the model with some attenuation of effect. When BMI at age 60-64y was also included there was a varying degree of attenuation of the effect at the different ages and increased BMI at age 36y remained associated with greater LAVI.

The effect of BMI at different ages on systolic function was also examined (Tables 7.2f-g).

In a minimally adjusted model, increased BMI at age 26y was associated with a decrease in EF i.e. worse systolic function (Table 7.2f). This association remained on further adjustments with a small increase in the magnitude of the effect with these adjustments.

In a minimally adjusted model, increased BMI at age 43y was associated with increased s' i.e. better systolic function (Table 7.2g). This association remained when SBP and T2DM at age 60-64y were included in the model and on inclusion of LVMI. Although the effect size continued to increase slightly with each round of adjustment, the association became non-significant when BMI at age 60-64y was included. The effect sizes for the associations between BMI at age 53y and s' were similar in the 4 models (minimally adjusted and then subsequent adjustments as described above). However, while 3 of the models showed non-significant associations, increased BMI at age 53y was associated with increased s' when the minimally adjusted model was also adjusted for SBP and T2DM at age 60-64y.

Table 7.2a. Regression coefficients, 95% confidence intervals and p values estimating the effect of body mass index at different ages on E/e' at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and body mass index at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1146)	0.0087 (-0.0370, 0.0544)	0.708	0.0037 (-0.0416, 0.0489)	0.874	-0.0065 (-0.0540, 0.0409)	0.787	-0.0726 (-0.1247, -0.0206)	0.006
26 (n=1213)	0.0617 (0.0209, 0.1026)	0.003	0.046 (0.0057, 0.0871)	0.025	0.0238 (-0.0191, 0.0667)	0.277	-0.0480 (-0.0985, 0.0026)	0.063
36 (n = 1250)	0.0876 (0.0530, 0.1222)	<0.001	0.0718 (0.0367, 0.1068)	<0.001	0.0590 (0.0222, 0.0958)	0.002	0.00048 (-0.0507, 0.0517)	0.985
43 (n = 1296)	0.0894 (0.0601, 0.1187)	<0.001	0.0724 (0.0425, 0.1022)	<0.001	0.0674 (0.0357, 0.0992)	<0.001	0.0083 (-0.0423, 0.0591)	0.748
53 (n = 1311)	0.0805 (0.0558, 0.1053)	<0.001	0.0658 (0.0406, 0.0910)	<0.001	0.0570 (0.0304, 0.0837)	<0.001	-0.0058 (-0.0609, 0.0493)	0.836
60-64 (n = 1367)	0.0862 (0.0633, 0.1091)	<0.001	0.0694 (0.0462, 0.0927)	<0.001	0.0642 (0.0395, 0.0889)	<0.001	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

Table 7.2b. Regression coefficients, 95% confidence intervals and p values estimating the effect of body mass index at different ages on E/A at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and body mass index at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1205)	-0.0081 (-0.0142, -0.0021)	0.009	-0.0086 (-0.0147, -0.0026)	0.005	-0.0075 (-0.0140, -0.0010)	0.023	-0.00024 (-0.0074, 0.0069)	0.947
26 (n=1279)	-0.0077 (-0.0132, -0.0023)	0.006	-0.0080 (-0.0135, -0.0024)	0.005	-0.0066 (-0.01252, -0.00061)	0.031	0.0043 (-0.0027, 0.0113)	0.229
36 (n = 1321)	-0.0114 (-0.0160, -0.0067)	<0.001	-0.0115 (-0.0163, -0.0068)	<0.001	-0.0103 (-0.0154, -0.0052)	<0.001	0.00079 (-0.00626, 0.00785)	0.826
43 (n = 1373)	-0.0114 (-0.0153, -0.0074)	<0.001	-0.0117 (-0.0158, -0.0076)	<0.001	-0.0106 (-0.0151, -0.0062)	<0.001	0.0012 (-0.0058, 0.0082)	0.743
53 (n = 1387)	-0.0097 (-0.0130, -0.0064)	<0.001	-0.0100 (-0.0135, -0.0066)	<0.001	-0.0097 (-0.0134, -0.0060)	<0.001	0.0017 (-0.0059, 0.0093)	0.661
60-64 (n = 1444)	-0.0115 (-0.0145, -0.0084)	<0.001	-0.0113 (-0.0144, -0.0081)	<0.001	-0.0110 (-0.0143, -0.0075)	<0.001	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

Table 7.2c. Regression coefficients, 95% confidence intervals and p values estimating the effect of body mass index at different ages on e' at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and body mass index at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1178)	-0.0080 (-0.0500, 0.0336)	0.707	-0.0115 (-0.0531, 0.0300)	0.587	-0.0014 (-0.0450, 0.0423)	0.951	0.0408 (-0.0076, 0.0891)	0.098
26 (n=1249)	-0.0298 (-0.0668, 0.0072)	0.114	-0.0267 (-0.0640, 0.0105)	0.159	-0.0120 (-0.0513, 0.0273)	0.548	0.0432 (-0.0034, 0.0897)	0.069
36 (n = 1283)	-0.0516 (-0.0832, -0.0200)	0.001	-0.0484 (-0.0807, -0.0161)	0.003	-0.0373 (-0.0713, -0.0034)	0.031	0.0082 (-0.0392, 0.0557)	0.734
43 (n = 1331)	-0.0521 (-0.0789, -0.0253)	<0.001	-0.0504 (-0.0780, -0.0228)	<0.001	-0.0431 (-0.0725, -0.0137)	0.004	0.0086 (-0.0385, 0.0558)	0.719
53 (n = 1348)	-0.0471 (-0.0696, -0.0245)	<0.001	-0.0452 (-0.0684, -0.0219)	<0.001	-0.0350 (-0.0597, -0.0103)	0.006	0.0292 (-0.0215, 0.0800)	0.259
60-64 (n = 1406)	-0.0592 (-0.0802, -0.0382)	<0.001	-0.0530 (-0.0746, -0.0315)	<0.001	-0.0467 (-0.0697, -0.0237)	<0.001	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

Table 7.2d. Regression coefficients, 95% confidence intervals and p values estimating the effect of body mass index at different ages on e'/a' at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and body mass index at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1158)	-0.00089 (-0.00594, 0.00416)	0.730	-0.00102 (-0.00603, 0.00400)	0.691	-0.00031 (-0.00561, 0.00498)	0.907	0.00790 (0.00210, 0.01369)	0.008
26 (n=1227)	-0.00506 (-0.00959,-0.00053)	0.029	-0.00429 (-0.00884, 0.00027)	0.065	-0.00286 (-0.00772, 0.00200)	0.248	0.00745 (0.00176, 0.01314)	0.010
36 (n = 1263)	-0.00921 (-0.01305, -0.00537)	<0.001	-0.00844 (-0.01235, -0.00453)	<0.001	-0.00786 (-0.01199, -0.00374)	<0.001	0.00165 (-0.00407, 0.00737)	0.572
43 (n = 1310)	-0.00901 (-0.01226, -0.00575)	<0.001	-0.00851 (-0.01185, -0.00516)	<0.001	-0.00824 (-0.01184, -0.00465)	<0.001	0.00260 (-0.00314, 0.00834)	0.374
53 (n = 1326)	-0.00902 (-0.01175, -0.00629)	<0.001	-0.00856 (-0.01136, -0.00575)	<0.001	-0.00812 (-0.01111, -0.00513)	<0.001	0.00101 (-0.00513, 0.00715)	0.747
60-64 (n = 1383)	-0.01032 (-0.01286, -0.00778)	<0.001	-0.00942 (-0.01202, -0.00682)	<0.001	-0.00928 (-0.01207, -0.00649)	<0.001	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

Table 7.2e. Regression coefficients, 95% confidence intervals and p values estimating the effect of body mass index at different ages on left atrial volume indexed to body surface area at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and body mass index at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1075)	0.276 (0.117, 0.435)	0.001	0.270 (0.109, 0.430)	0.001	0.148 (-0.016, 0.313)	0.077	0.018 (-0.165, 0.200)	0.847
26 (n=1142)	0.449 (0.306, 0.591)	<0.001	0.445 (0.300, 0.590)	<0.001	0.282 (0.132, 0.431)	<0.001	0.161 (-0.017, 0.338)	0.076
36 (n = 1176)	0.495 (0.372, 0.618)	<0.001	0.488 (0.361, 0.614)	<0.001	0.340 (0.211, 0.470)	<0.001	0.310 (0.132, 0.488)	0.001
43 (n = 1219)	0.363 (0.259, 0.467)	<0.001	0.358 (0.250, 0.466)	<0.001	0.227 (0.116, 0.338)	<0.001	0.161 (-0.010, 0.333)	0.066
53 (n = 1236)	0.289 (0.199, 0.379)	<0.001	0.285 (0.192, 0.379)	<0.001	0.166 (0.070, 0.262)	0.001	0.021 (-0.171, 0.213)	0.830
60-64 (n = 1287)	0.286 (0.202, 0.370)	<0.001	0.276 (0.189, 0.362)	<0.001	0.173 (0.084, 0.263)	<0.001	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

Table 7.2f. Regression coefficients, 95% confidence intervals and p values estimating the effect of body mass index at different ages on ejection fraction at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and body mass index at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1123)	-0.16 (-0.38, 0.05)	0.137	-0.15 (-0.37, 0.06)	0.163	-0.19 (-0.41, 0.04)	0.100	-0.18 (-0.43, 0.06)	0.142
26 (n=1194)	-0.23 (-0.43, -0.04)	0.017	-0.23 (-0.42, -0.03)	0.023	-0.24 (-0.44, -0.05)	0.016	-0.34 (-0.58, -0.10)	0.005
36 (n = 1224)	-0.09 (-0.25, 0.07)	0.279	-0.06 (-0.23, 0.10)	0.450	-0.09 (-0.26, 0.08)	0.304	-0.10 (-0.34, 0.14)	0.396
43 (n = 1279)	-0.07 (-0.21, 0.07)	0.355	-0.05 (-0.19, 0.10)	0.505	-0.08 (-0.23, 0.07)	0.274	-0.07 (-0.30, 0.17)	0.585
53 (n = 1293)	-0.04 (-0.16, 0.08)	0.516	-0.02 (-0.14, 0.10)	0.769	-0.03 (-0.16, 0.09)	0.627	0.07 (-0.19, 0.32)	0.599
60-64 (n = 1343)	-0.05 (-0.16, 0.06)	0.418	-0.04 (-0.15, 0.08)	0.517	-0.05 (-0.17, 0.06)	0.371	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

Table 7.2g. Regression coefficients, 95% confidence intervals and p values estimating the effect of body mass index at different ages on s' at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and body mass index at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1156)	0.019 (-0.017, 0.054)	0.300	0.019 (-0.017, 0.055)	0.308	0.021 (-0.016, 0.058)	0.261	0.015 (-0.026, 0.056)	0.482
26 (n=1223)	0.023 (-0.009, 0.054)	0.154	0.025 (-0.0073, 0.0571)	0.129	0.031 (-0.0023, 0.0646)	0.068	0.031 (-0.008, 0.071)	0.123
36 (n = 1260)	0.208 (-0.006, 0.048)	0.131	0.023 (-0.0046, 0.0514)	0.101	0.022 (-0.0069, 0.0511)	0.136	0.0064 (-0.034, 0.047)	0.759
43 (n = 1307)	0.025 (0.002, 0.048)	0.032	0.029 (0.0053, 0.0529)	0.017	0.028 (0.0031, 0.0529)	0.028	0.038 (-0.0021, 0.0779)	0.063
53 (n = 1324)	0.017 (-0.003, 0.036)	0.089	0.021 (0.0008, 0.0408)	0.042	0.019 (-0.002, 0.040)	0.083	0.022 (-0.021, 0.064)	0.325
60-64 (n = 1383)	0.010 (-0.008, 0.028)	0.280	0.013 (-0.0053, 0.0317)	0.162	0.012 (-0.0070, 0.0320)	0.210	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

The effect of overweight (BMI>=25 kg/m^2) at different ages on cardiac function is presented in Tables 7.3a-3g.

Overweight from the age of 26y onwards was associated with increased E/e' i.e. worse diastolic function in a minimally adjusted model (Table 7.3a); this remained the case when SBP and T2DM at age 60-64y were included and the association held from the age of 36y onwards when LVMI was included in the model. There was a minor attenuation in effect with each successive adjustment. When overweight at age 60-64y was included in the models there was further attenuation of the effects and only overweight at 43y was associated with increased E/e'.

The associations between overweight and E/A were qualitatively similar to that between overweight and E/e'. The only difference was that in the final model, when overweight at 60-64y was included, only overweight at 53y remained associated with decreased E/A. Overweight at 43y was marginally non-significant in the final model (Table 7.3b).

Overweight from the age of 36y onwards was associated decreased e' i.e. poorer diastolic function in a minimally adjusted model (Table 7.3c); this was also the case when SBP and T2DM at age 60-64y and LVMI were included with minimal changes in effect sizes with these adjustments. In a fully adjusted model including overweight at 60-64y, only overweight at 43y was associated with e' with a near-halving of effect size.

The association between overweight and e'/a' (Table 7.3d) mirrored that between overweight and e'.

In a minimally adjusted model, overweight from 20y onwards was associated with increased LAVI (Table 7.3e); this was also the case on inclusion of SBP and T2DM at age 60-64y. When LVMI was included, there was some attenuation of the effect and the associations held from age 26y onwards. In a fully-adjusted model, there was further attenuation of the effect and only overweight at age 43y remained associated with increased LAVI.

Overweight at ages 26y and 36y was associated with decreased EF i.e. worse systolic function in a minimally adjusted model (Table 7.3f). These associations remained on further adjustments [except when SBP and T2DM at age 60-64y were added into the overweight at age 26y model where it was borderline non-significant ($p = 0.05$)].

Overweight at different ages was not associated with s' (Table 7.3g). The associations with overweight at age 43y came the closest to significance (positive association i.e. better systolic function).

Table 7.3a. Regression coefficients, 95% confidence intervals and p values estimating the effect of overweight at different ages on E/e' at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and overweight at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + overweight at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1085)	0.325 (-0.054, 0.705)	0.093	0.286 (-0.088, 0.659)	0.133	0.217 (-0.178, 0.613)	0.281	0.085 (-0.313, 0.482)	0.675
26 (n=1168)	0.523 (0.201, 0.844)	0.001	0.409 (0.090, 0.729)	0.012	0.267 (-0.075, 0.609)	0.126	0.117 (-0.231, 0.466)	0.508
36 (n = 1218)	0.474 (0.219, 0.729)	<0.001	0.353 (0.098, 0.609)	0.007	0.315 (0.046, 0.583)	0.022	0.169 (-0.113, 0.451)	0.241
43 (n = 1286)	0.587 (0.362, 0.813)	<0.001	0.456 (0.230, 0.681)	<0.001	0.492 (0.253, 0.730)	<0.001	0.312 (0.050, 0.575)	0.020
53 (n = 1309)	0.491 (0.259, 0.723)	<0.001	0.350 (0.119, 0.581)	0.003	0.261 (0.020, 0.502)	0.034	-0.087 (-0.388, 0.215)	0.573
60-64 (n = 1362)	0.887 (0.655, 1.119)	<0.001	0.710 (0.476, 0.943)	<0.001	0.603 (0.357, 0.849)	<0.001	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area

Table 7.3b. Regression coefficients, 95% confidence intervals and p values estimating the effect of overweight at different ages on E/A at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and overweight at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + overweight at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1143)	-0.049 (-0.099, 0.001)	0.056	-0.049 (-0.099, 0.001)	0.055	-0.058 (-0.1112, -0.0041)	0.035	-0.037 (-0.091, 0.017)	0.179
26 (n=1233)	-0.051 (-0.093, -0.008)	0.019	-0.051 (-0.093, -0.008)	0.020	-0.046 (-0.093, 0.001)	0.053	-0.019 (-0.066, 0.028)	0.430
36 (n = 1288)	-0.061 (-0.094, -0.027)	<0.001	-0.058 (-0.093, -0.024)	0.001	-0.056 (-0.093, -0.020)	0.003	-0.028 (-0.067, 0.010)	0.148
43 (n = 1361)	-0.078 (-0.108, -0.048)	<0.001	-0.076 (-0.107, -0.045)	<0.001	-0.067 (-0.100, -0.034)	<0.001	-0.035 (-0.071, 0.001)	0.058
53 (n = 1385)	-0.086 (-0.117, -0.055)	<0.001	-0.081 (-0.112, -0.050)	<0.001	-0.084 (-0.117, -0.051)	<0.001	-0.046 (-0.087, -0.004)	0.031
60-64 (n = 1439)	-0.101 (-0.132, -0.070)	<0.001	-0.095 (-0.126, -0.063)	<0.001	-0.093 (-0.127, -0.059)	<0.001	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area

Table 7.3c. Regression coefficients, 95% confidence intervals and p values estimating the effect of overweight at different ages on e' at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and overweight at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + overweight at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1114)	-0.220 (-0.560, 0.120)	0.204	-0.229 (0.568, 0.109)	0.184	-0.190 (-0.548, 0.168)	0.297	-0.076 (-0.436, 0.284)	0.678
26 (n=1201)	-0.170 (-0.461, 0.120)	0.251	-0.142 (-0.435, 0.151)	0.341	-0.085 (-0.398, 0.228)	0.593	0.056 (-0.262, 0.374)	0.729
36 (n = 1251)	-0.383 (-0.614, -0.153)	0.001	-0.349 (-0.581, -0.116)	0.003	-0.326 (-0.572, -0.080)	0.009	-0.191 (-0.449, 0.067)	0.147
43 (n = 1321)	-0.461 (-0.667, -0.255)	<0.001	-0.428 (-0.636, -0.220)	<0.001	-0.438 (-0.659, -0.218)	<0.001	-0.261 (-0.504, -0.018)	0.036
53 (n = 1346)	-0.482 (-0.692, -0.271)	<0.001	-0.420 (-0.632, -0.208)	<0.001	-0.364 (-0.586, -0.141)	<0.001	-0.093 (-0.372, 0.186)	0.514
60-64 (n = 1401)	-0.714 (-0.926, -0.503)	<0.001	-0.629 (-0.844, -0.414)	<0.001	-0.560 (-0.788, -0.333)	<0.001	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area

Table 7.3d. Regression coefficients, 95% confidence intervals and p values estimating the effect of overweight at different ages on e'/a' at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and overweight at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + overweight at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1095)	-0.031 (-0.073, 0.010)	0.136	-0.031 (-0.072, 0.009)	0.131	-0.032 (-0.075, 0.012)	0.154	-0.011 (-0.055, 0.032)	0.612
26 (n=1180)	-0.028 (-0.064, 0.007)	0.120	-0.023 (-0.059, 0.128)	0.209	-0.018 (-0.057, 0.020)	0.349	0.0062 (-0.033, 0.045)	0.753
36 (n = 1232)	-0.054 (-0.083, -0.026)	<0.001	-0.048 (-0.076, -0.019)	0.001	-0.051 (-0.081, -0.021)	0.001	-0.026 (-0.058, 0.005)	0.103
43 (n = 1300)	-0.074 (-0.099, -0.049)	<0.001	-0.068 (-0.093, -0.043)	<0.001	-0.070 (-0.097, -0.043)	<0.001	-0.040 (-0.070, -0.011)	0.008
53 (n = 1324)	-0.081 (-0.107, -0.056)	<0.001	-0.072 (-0.098, -0.047)	<0.001	-0.073 (-0.100, -0.046)	<0.001	-0.031 (-0.065, 0.0033)	0.076
60-64 (n = 1378)	-0.104 (-0.130, -0.079)	<0.001	-0.093 (-0.119, -0.067)	<0.001	-0.092 (-0.120, -0.064)	<0.001	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area

Table 7.3e. Regression coefficients, 95% confidence intervals and p values estimating the effect of overweight at different ages on left atrial volume indexed to body surface area at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and overweight at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + overweight at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1019)	1.938 (0.677, 3.198)	0.003	1.900 (0.637, 3.162)	0.003	1.246 (-0.051, 2.543)	0.060	0.807 (-0.503, 2.116)	0.227
26 (n=1097)	2.619 (1.522, 3.717)	<0.001	2.601 (1.488, 3.714)	<0.001	1.493 (0.331, 2.655)	0.012	1.073 (-0.112, 2.259)	0.076
36 (n = 1147)	2.421 (1.528, 3.314)	<0.001	2.285 (1.377, 3.193)	<0.001	1.392 (0.459, 2.325)	0.003	0.928 (-0.057, 1.914)	0.065
43 (n = 1208)	2.514 (1.728, 3.300)	<0.001	2.407 (1.603, 3.210)	<0.001	1.552 (0.729, 2.375)	<0.001	1.087 (0.181, 1.993)	0.019
53 (n = 1235)	2.430 (1.627, 3.232)	<0.001	2.340 (1.526, 3.155)	<0.001	1.606 (0.775, 2.437)	<0.001	0.883 (-0.160, 1.927)	0.097
60-64 (n = 1283)	2.823 (2.001, 3.645)	<0.001	2.738 (1.898, 3.578)	<0.001	1.803 (0.940, 2.667)	<0.001	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area

Table 7.3f. Regression coefficients, 95% confidence intervals and p values estimating the effect of overweight at different ages on ejection fraction at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and overweight at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + overweight at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1060)	-0.057 (-1.820, 1.707)	0.950	0.0078 (-1.769, 1.785)	0.993	-0.0046 (-1.8028, 1.7937)	0.996	-0.140 (-1.969, 1.689)	0.881
26 (n=1147)	-1.602 (-3.126, -0.077)	0.040	-1.540 (-3.082, 0.002)	0.050	-1.568 (-3.125, -0.011)	0.048	-1.879 (-3.476, -0.283)	0.021
36 (n = 1192)	-1.575 (-2.789, -0.361)	0.011	-1.401 (-2.633, -0.169)	0.026	-1.524 (-2.770, -0.277)	0.017	-1.963 (-3.276, -0.649)	0.003
43 (n = 1266)	-0.335 (-1.414, 0.744)	0.543	-0.276 (-1.375, 0.822)	0.622	-0.451 (-1.568, 0.667)	0.429	-0.779 (-2.015, 0.457)	0.216
53 (n = 1291)	-0.277 (-1.364, 0.811)	0.618	-0.118 (-1.219, 0.984)	0.834	-0.168 (-1.287, 0.951)	0.768	-0.846 (-2.262, 0.571)	0.242
60-64 (n = 1339)	0.525 (-0.586, 1.636)	0.354	0.562 (-0.576, 1.699)	0.333	0.483 (-0.678, 1.644)	0.414	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area

Table 7.3g. Regression coefficients, 95% confidence intervals and p values estimating the effect of overweight at different ages on s' at age 60-64y. Models adjusted for age, sex and clinic attended. Subsequent adjustments made for systolic blood pressure and presence of type 2 diabetes mellitus at age 60-64y, left ventricular mass indexed to body surface area and overweight at age 60-64y.

Age (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP and T2DM at 60-64y)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + overweight at 60-64y)	
	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value	β (95%CI)	p value
20 (n=1094)	0.019 (-0.273, 0.311)	0.897	0.024 (-0.270, 0.318)	0.874	0.046 (-0.259, 0.352)	0.767	0.052 (-0.258, 0.362)	0.741
26 (n=1176)	-0.023 (-0.271, 0.225)	0.855	-0.021 (-0.275, 0.232)	0.870	0.047 (-0.221, 0.316)	0.730	0.061 (-0.214, 0.335)	0.664
36 (n = 1230)	-0.035 (-0.233, 0.163)	0.729	-0.021 (-0.223, 0.181)	0.841	0.006 (-0.205, 0.217)	0.956	-0.005 (-0.228, 0.217)	0.964
43 (n = 1297)	0.149 (-0.026, 0.324)	0.095	0.175 (-0.005, 0.354)	0.056	0.138 (-0.049, 0.326)	0.148	0.195 (-0.014, 0.403)	0.067
53 (n = 1322)	0.092 (-0.087, 0.271)	0.312	0.119 (-0.063, 0.302)	0.199	0.097 (-0.092, 0.285)	0.315	0.160 (-0.079, 0.400)	0.189
60-64 (n = 1378)	-0.067 (-0.249, 0.114)	0.467	-0.038 (-0.224, 0.148)	0.690	-0.054 (-0.248, 0.139)	0.581	-	-

SBP- Systolic blood pressure; T2DM – Type 2 diabetes mellitus, LVMI - Left ventricular mass indexed to body surface area

There was an overall significant linear trend of increase in E/e' (i.e. implying worse diastolic function) with earlier age at first overweight (Table 7.4a, Figure 7.1a). The test for deviation from linear trend was non-significant (p = 0.3757).This was maintained when SBP, T2DM and LVMI at age 60-64y were included in the model with some attenuation of effect at each round of adjustment. When BMI at 60-64y was included in the model, regression coefficients for each of the ages became negative (i.e. indicating better diastolic function). However, the overall test for linear trend was non–significant.

There was an overall significant linear trend of decreased E/A (i.e. implying worse diastolic function) with earlier age at first overweight in all models (Table 7.4b, Figure 7.1b). The test for deviation from linear trend was significant (p = 0.0145).There was an attenuation of the trend when BMI at age 60-64y as included in the model but the trend remained.

When the association between age at first overweight and e' was investigated, there was an overall significant linear trend demonstrating greater decrease in e' (i.e. implying worse diastolic function) the earlier age at first overweight, in the minimally adjusted model (Table 7.4c, Figure 7.1c). The test for deviation from linear trend was significant (p = 0.0374).The linear trend remained on inclusion of SBP, T2DM and LVMI at age 60-64y. The trend was substantially attenuated and became non-significant when BMI at 60-64y was included. The coefficient at age 26y became positive (i.e. implying better diastolic function) although it was non-significant.

There was an overall significant linear trend of decrease in e'/a' (i.e. implying worse diastolic function) with earlier age at first overweight (Table 7.4d, Figure 7.1d). The test for deviation from linear trend was significant (p = 0.0002). This was maintained when SBP, T2DM and LVMI at age 60-64y were included in the model. The coefficients were attenuated when BMI at 60-64y was included in the model and the overall linear trend became non-significant.

There was an overall significant linear trend of increase in LAVI with earlier age at first overweight (Table 7.4e, Figure 7.1e). The test for deviation from linear trend was non-significant (p = 0.0924). This was maintained when SBP, T2DM and LVMI at age 60-64y were included in the model. There was only a small change in the regression coefficients when BMI at age 60-64y was included and the overall linear trend just became non-significant.

There was no significant overall linear trend between EF and age at first overweight in any of the models (Table 7.4f, Figure 7.1f). The test for deviation from linear trend was non-significant (p = 0.5422). The regression coefficient for age at first overweight at 43y was significant on adjusting for SBP and T2DM at age 60-64y and when LVMI was included in the model, but was non-significant in the minimally and fully adjusted models. The test for deviation from linear trend was non-significant (p = 0.1919). Similarly, there was no relationship between s' and age at first overweight (Table 7.4g, Figure 7.1g).

Table 7.4a. Regression coefficients, 95% confidence intervals and p values estimating the effect of age at first overweight on E/e' at 60-64 years in men and women.

Age at first diagnosis of being overweight (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP at 60-64y + T2DM)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	B (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend
20	0.965 (0.369, 1.562)	<0.001	0.828 (0.224, 1.432)	<0.001	0.573 (-0.059, 1.205)	0.002	-0.650 (-1.540, 0.239)	0.387
26	1.288 (0.647, 1.930)		1.065 (0.400, 1.730)		0.826 (0.116, 1.535)		-0.286 (-1.193, 0.622)	
36	1.008 (0.496, 1.519)		0.839 (0.318, 1.360)		0.796 (0.259, 1.333)		-0.081 (-0.779, 0.618)	
43	0.792 (0.124, 1.025)		0.639 (0.139, 1.140)		0.581 (0.065, 1.096)		-0.060 (-0.668, 0.548)	
53	0.575 (0.124, 1.025)		0.466 (0.008, 0.923)		0.234 (-0.234, 0.702)		-0.237 (-0.761, 0.286)	
60-64	0.444 (-0.139, 1.027)		0.351 (-0.233, 0.936)		0.213 (-0.394, 0.820)		-0.143 (-0.771, 0.485)	

SBP - Systolic blood pressure; T2DM - Type 2 Diabetes mellitus; LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

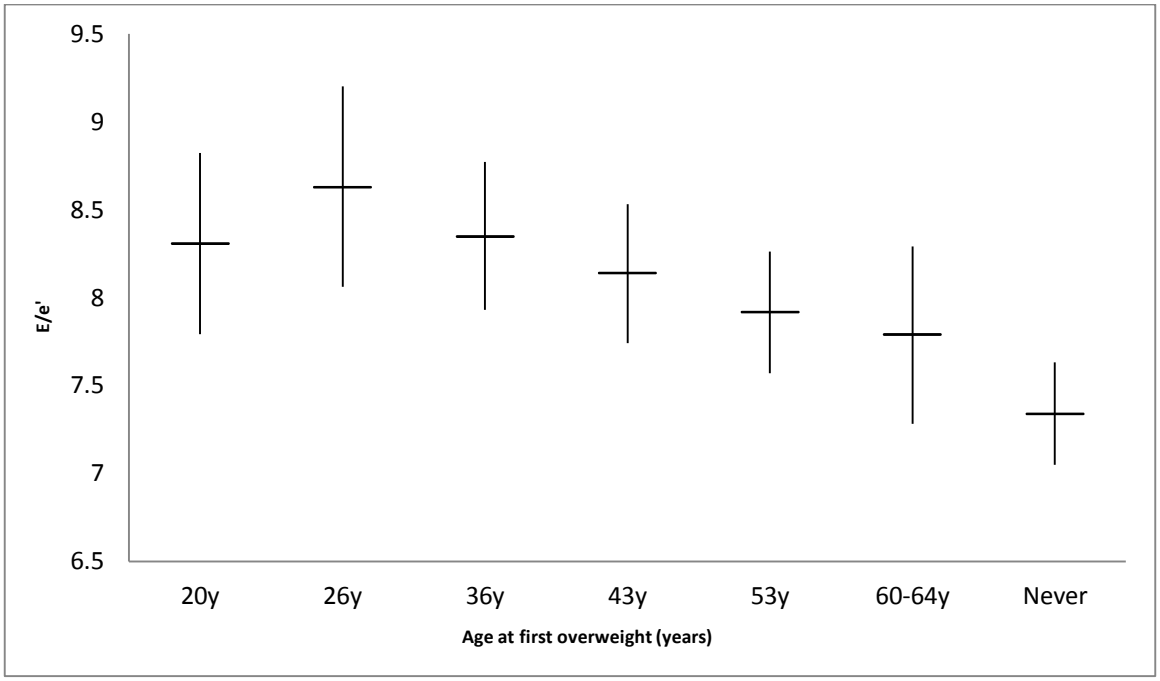


Figure 7.1a. Estimated marginal means in men and women of E/e' for different ages at first overweight and for never overweight for model 1 (above).

Table 7.4b. Regression coefficients, 95% confidence intervals and p values estimating the effect of duration of age at first diagnosis of being persistently overweight on E/A at 60-64 years in men and women.

Age at first diagnosis of being overweight (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP at 60-64y + T2DM)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend
20	-0.194 (-0.273, -0.115)	<0.001	-0.188 (-0.268, -0.109)	<0.001	-0.181 (-0.267, 0.095)	<0.001	-0.170 (-0.295, -0.046)	0.020
26	-0.123 (-0.208, -0.039)		-0.115 (-0.203, -0.028)		-0.117 (-0.215, -0.018)		-0.108 (-0.235, 0.019)	
36	-0.150 (-0.218, -0.083)		-0.141 (-0.210, -0.072)		-0.126 (-0.200, -0.052)		-0.119 (-0.216, -0.021)	
43	-0.162 (-0.228, -0.096)		-0.149 (-0.216, -0.083)		-0.136 (-0.208, -0.064)		-0.131 (-0.217, -0.045)	
53	-0.116 (-0.176, -0.056)		-0.104 (-0.165, 0.043)		-0.094 (-0.159, -0.030)		-0.090 (-0.164, -0.017)	
60-64	-0.088 (-0.165, -0.010)		-0.077 (-0.154, 0.001)		-0.057 (-0.141, 0.026)		-0.054 (-0.142, 0.033)	

SBP - Systolic blood pressure; T2DM - Type 2 Diabetes mellitus; LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

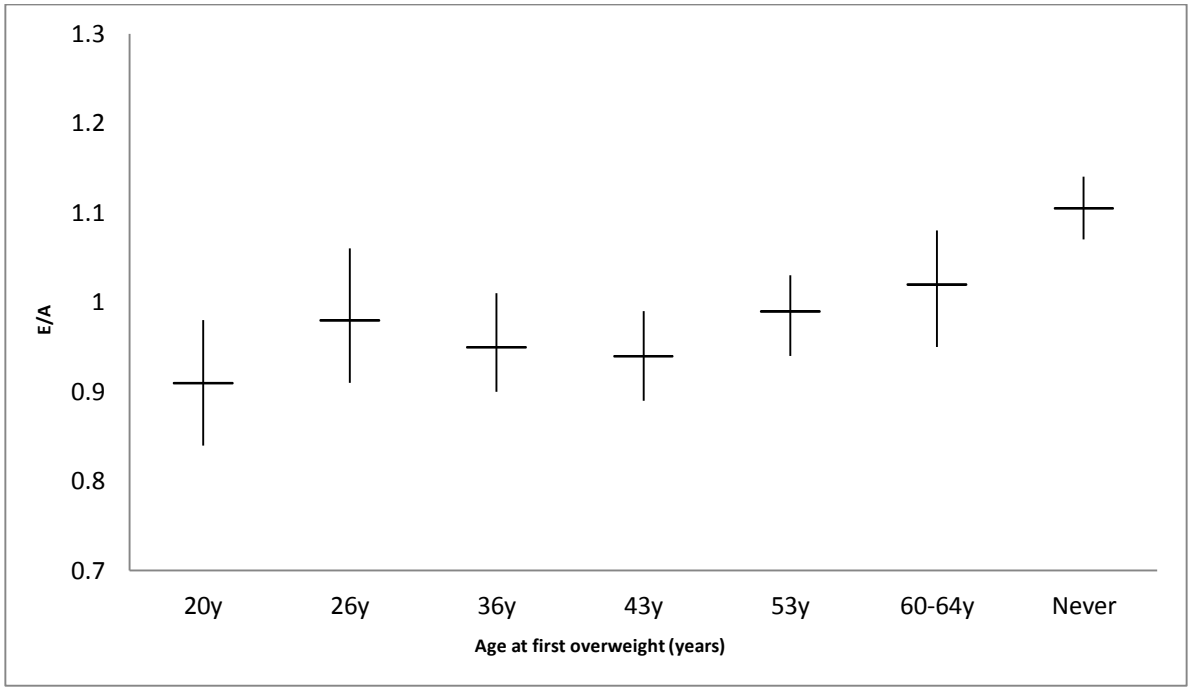


Figure 7.1b. Estimated marginal means in men and women of E/A for different ages at first overweight and for never overweight for model 1 (above).

Table 7.4c. Regression coefficients, 95% confidence intervals and p values estimating the effect of duration of age at first diagnosis of being persistently overweight on e' at 60-64 years in men and women.

Age at first diagnosis of being overweight (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP at 60-64y + T2DM)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend
20	-0.745 (-1.264, 0.226)	<0.001	-0.710 (-1.237, -0.183)	0.001	-0.377 (-0.917, 0.163)	0.005	-0.115 (-0.906, 0.677)	0.843
26	-0.635 (-1.206, -0.064)		-0.579 (-1.170, 0.012)		-0.406 (-1.040, 0.228)		0.043 (-0.772, 0.859)	
36	-0.977 (-1.427, -0.526)		-0.898 (-1.357, -0.440)		-0.877 (-1.354, -0.401)		-0.524 (-1.149, 0.101)	
43	-0.755 (-1.189, -0.321)		-0.661 (-1.103, -0.176)		-0.639 (-1.098, -0.181)		-0.383 (-0.926, 0.161)	
53	-0.672 (-1.070, -0.275)		-0.580 (-0.983, -0.176)		-0.435 (-0.849, -0.021)		-0.245 (-0.712, 0.222)	
60-64	-0.485 (-1.000, 0.030)		-0.407 (-0.923, 0.110)		-0.377 (-0.017, 0.163)		-0.234 (-0.797, 0.329)	

SBP - Systolic blood pressure; T2DM - Type 2 Diabetes mellitus; LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

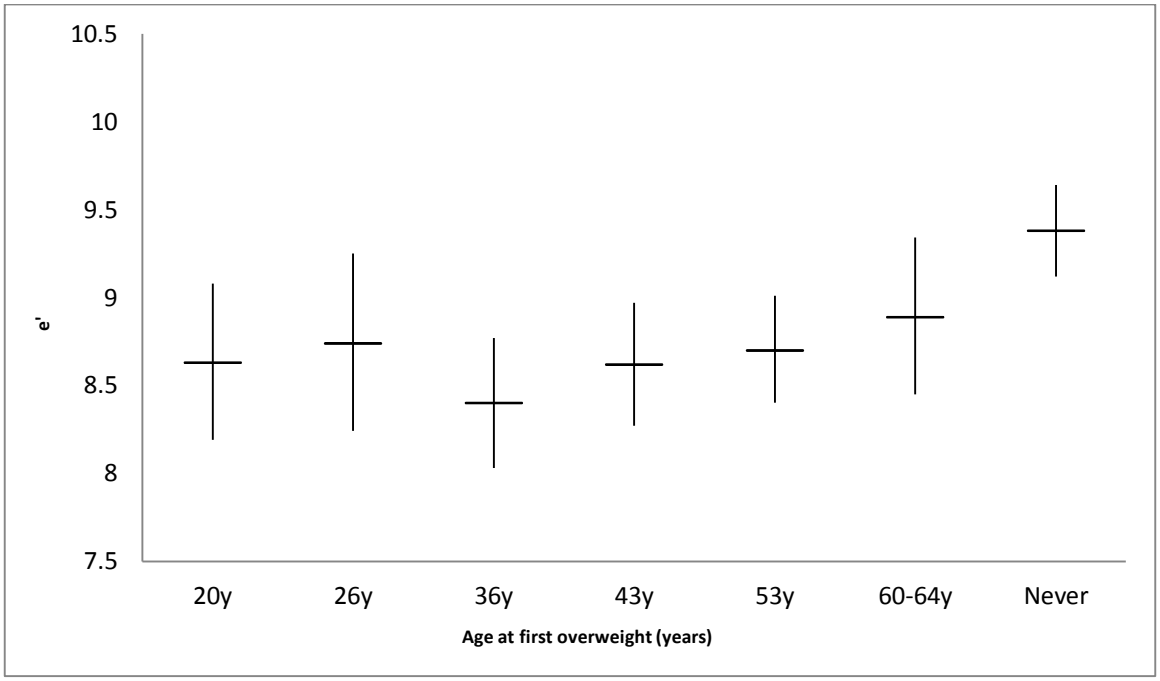


Figure 7.1c. Estimated marginal means in men and women of e' for different ages at first overweight and for never overweight for model 1 (above).

Table 7.4d. Regression coefficients, 95% confidence intervals and p values estimating the effect of duration of age at first diagnosis of being persistently overweight on e'/a' at 60-64 years in men and women.

Age at first diagnosis of being overweight (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP at 60-64y + T2DM†)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend
20	-0.135 (-0.198, -0.073)	<0.001	-0.124 (-0.187, -0.061)	<0.001	-0.125 (-0.193, -0.058)	<0.001	-0.059 (-0.155, 0.038)	0.416
26	-0.082 (-0.151, -0.013)		-0.062 (-0.133, 0.009)		-0.064 (-0.143, 0.014)		-0.004 (-0.105, 0.096)	
36	-0.162 (-0.216, -0.107)		-0.146 (-0.201, -0.090)		-0.156 (-0.215, -0.097)		-0.109 (-0.185, -0.032)	
43	-0.135 (-0.187, -0.083)		-0.117 (-0.170, -0.064)		-0.124 (-0.180, -0.068)		-0.090 (-0.156, -0.023)	
53	-0.101 (-0.149, -0.052)		-0.084 (-0.132, -0.035)		-0.083 (-0.134, -0.032)		-0.057 (-0.1145, 0.0001)	
60-64	-0.087 (-0.150, -0.025)		-0.075 (-0.137, -0.012)		-0.075 (-0.142, 0.009)		-0.056 (-0.126, 0.013)	

SBP - Systolic blood pressure; T2DM - Type 2 Diabetes mellitus; LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

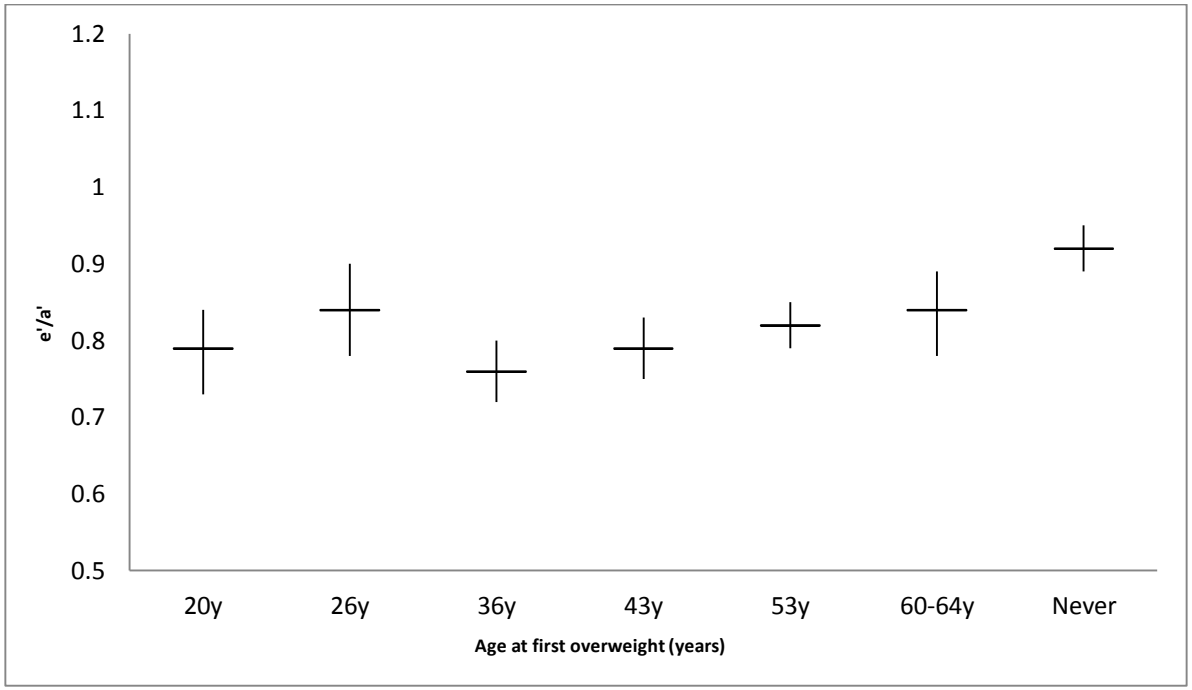


Figure 7.1d. Estimated marginal means in men and women of e'/a' for different ages at first overweight and for never overweight for model 1 (above).

Table 7.4e. Regression coefficients, 95% confidence intervals and p values estimating the effect of duration of age at first diagnosis of being persistently overweight on left atrial volume indexed to body surface area at 60-64 years in men and women.

Age at first diagnosis of being overweight (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP at 60-64y + T2DM)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend
20	5.458 (3.556, 7.361)	<0.001	5.485 (3.553, 7.417)	<0.001	3.625 (1.622, 5.627)	<0.001	3.703 (0.755, 6.651)	0.070
26	4.965 (2.857, 7.073)		4.944 (2.753, 7.135)		2.434 (0.104, 4.764)		2.504 (-0.529, 5.538)	
36	4.127 (2.412, 5.842)		4.087 (2.330, 5.845)		2.865 (1.083, 4.648)		2.921 (0.564, 5.278)	
43	3.317 (1.647, 4.987)		3.375 (1.663, 5.087)		2.282 (0.537, 4.028)		2.323 (0.244, 4.402)	
53	2.189 (0.706, 3.671)		2.284 (0.776, 3.791)		1.450 (-0.072, 2.971)		1.481 (-0.271, 3.232)	
60-64	2.917 (1.028, 4.806)		3.005 (1.106, 4.905)		2.346 (0.395, 4.297)		2.369 (0.311, 4.428)	

SBP - Systolic blood pressure; T2DM - Type 2 Diabetes mellitus; LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index index

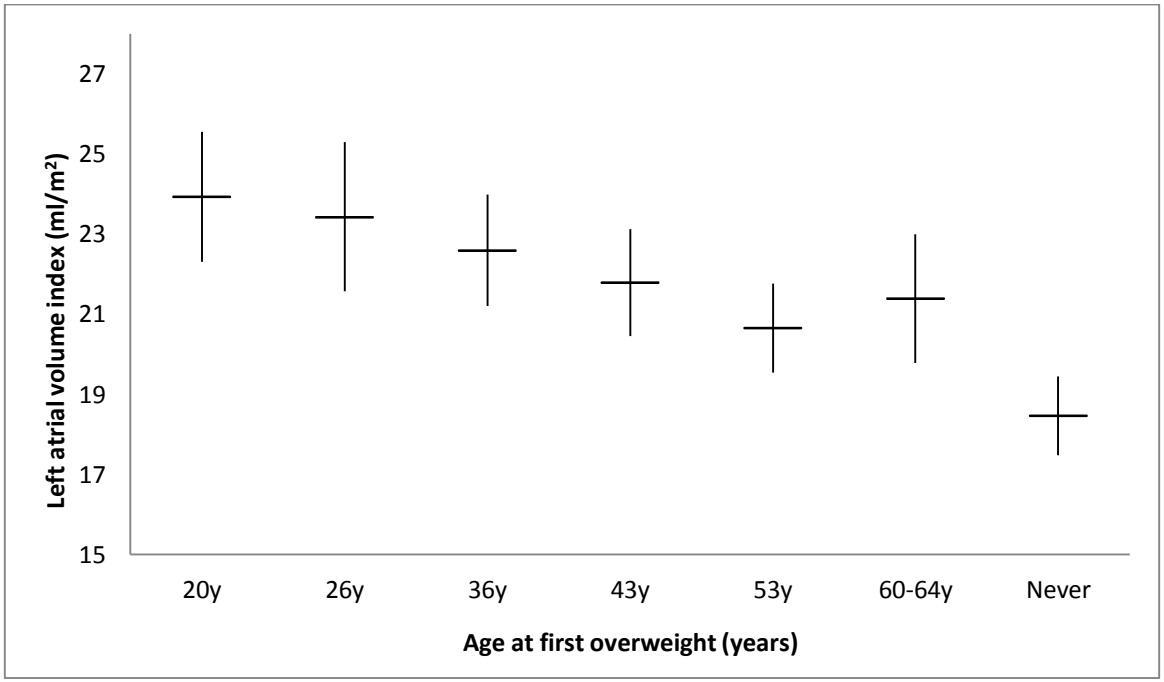


Figure 7.1e. Estimated marginal means in men and women of left atrial volume indexed to body surface area (ml/m^2) for different ages at first overweight and for never overweight for model 1 (above).

Table 7.4f. Regression coefficients (% Ejection Fraction), 95% confidence intervals and p values estimating the effect of age at first diagnosis of being persistently overweight on Ejection Fraction at 60-64 years in men and women.

Age at first diagnosis of being overweight (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP at 60-64y + T2DM)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend
20	-1.290 (-4.049, 1.470)	0.344	-1.142 (-3.967, 1.682)	0.416	-1.051 (-3.909, 1.806)	0.394	-2.122 (-6.302, 2.057)	0.152
26	-0.128 (-3.259, 3.003)		0.119 (-3.120, 3.357)		0.264 (-3.023, 3.551)		-0.694 (-4.966, 3.578)	
36	-0.081 (-2.472, 2.309)		0.109 (-2.351, 2.570)		-0.095 (-2.608, 2.418)		-0.852 (-4.163, 2.459)	
43	2.287 (-0.045, 4.619)		2.484 (0.090, 4.877)		2.575 (0.136, 5.014)		2.020 (-0.887, 4.927)	
53	1.103 (-0.997, 3.204)		1.294 (-0.852, 3.440)		1.442 (-0.733, 3.617)		1.019 (-1.468, 3.506)	
60-64	1.762 (-1.030, 4.553)		1.862 (-0.956, 4.679)		1.904 (-0.926, 4.733)		1.593 (-1.373, 4.559)	

SBP - Systolic blood pressure; T2DM - Type 2 Diabetes mellitus; LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

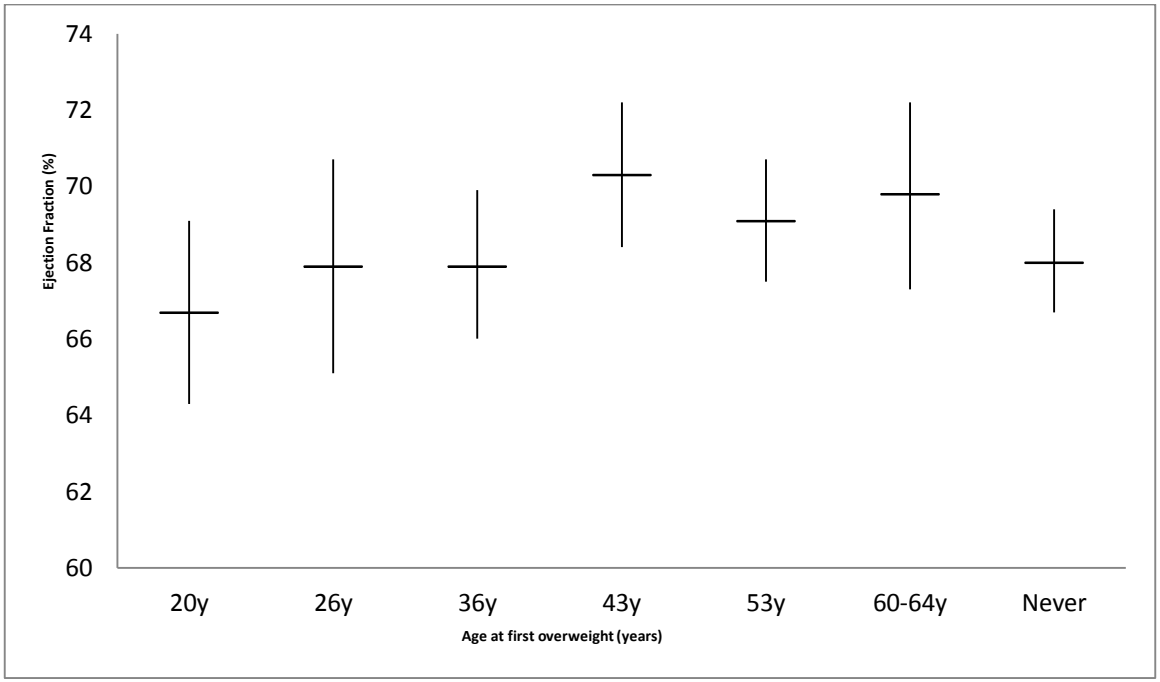


Figure 7.1f. Estimated marginal means in men and women of ejection fraction (%) for different ages at first overweight and for never overweight for model 1 (above).

Table 7.4g. Regression coefficients, 95% confidence intervals and p values estimating the effect of duration of age at first diagnosis of being persistently overweight on s' at 60-64 years in men and women.

Age at first diagnosis of being overweight (years)	Model 1 (age sex, clinic)		Model 2 (Model 1 + SBP at 60-64y + T2DM)		Model 3 (Model 2 + LVMI)		Model 4 (Model 3 + BMI at 60-64y)	
	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend	β (95%CI)	p value for overall linear trend
20	0.218 (-0.249, 0.684)	0.313	0.230 (-0.247, 0.707)	0.281	0.200 (-0.291, 0.691)	0.261	-0.009 (-0.713, 0.695)	0.833
26	0.001 (-0.519, 0.521)		0.023 (-0.523, 0.570)		0.228 (-0.359, 0.815)		0.043 (-0.697, 0.782)	
36	-0.008 (-0.411, 0.395)		0.008 (-0.404, 0.421)		0.060 (-0.360, 0.481)		-0.086 (-0.636, 0.464)	
43	0.347 (-0.041, 0.734)		0.352 (-0.045, 0.749)		0.266 (-0.138, 0.669)		0.158 (-0.321, 0.638)	
53	0.030 (-0.326, 0.387)		0.025 (-0.340, 0.389)		0.071 (-0.295, 0.438)		-0.007 (-0.420, 0.406)	
60-64	-0.111 (-0.571, 0.349)		-0.111 (-0.575, 0.353)		-0.047 (-0.522, 0.428)		-0.107 (-0.603, 0.390)	

SBP - Systolic blood pressure; T2DM - Type 2 Diabetes mellitus; LVMI - Left ventricular mass indexed to body surface area; BMI - Body mass index

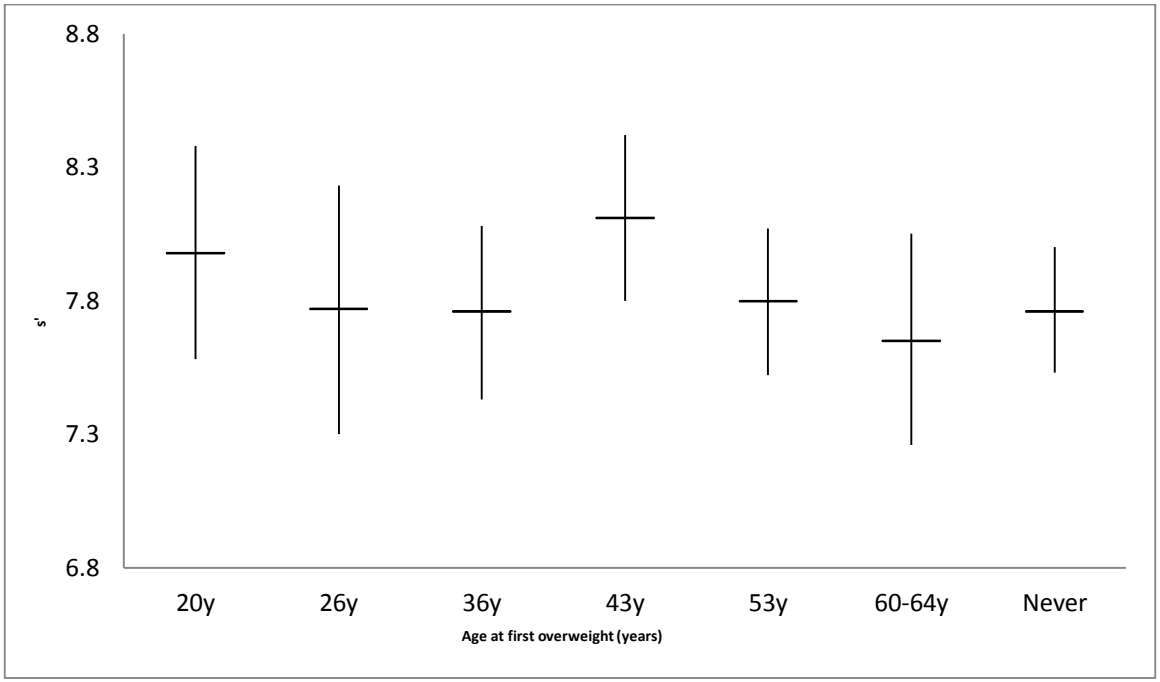


Figure 7.1g. Estimated marginal means in men and women of s' for different ages at first overweight and for never overweight for model 1 (above).

Discussion

We found that previous BMI/overweight and earlier age at first overweight were all associated with poorer subsequent diastolic function. However the relationships were complex and varied. Increased BMI from the twenties onwards was associated with diastolic dysfunction at age 60-64y. On adding in BMI at 60-64y, the association reversed and for ages 20y and 26y increased BMI was associated with poorer diastolic function (when measured in terms of E/e' and e'/a'). Overweight from the age of 26y (E/e' and E/A) or 36y onwards (e' and e'/a') was associated with poorer diastolic function at 60-64y. In fully adjusted models, overweight at 43y (E/e', e'/a' and e') and overweight at 53y (E/A) were associated with decreased diastolic function. On examining the effect of age at first overweight, we found that earlier age at first overweight was associated with worse diastolic function (E/e', E/A, e' and e'/a'). When BMI at age 60-64y was included, the overall linear trend remained significant for E/A only.

When the effects of BMI/overweight on LAVI were examined it was found that increased BMI and overweight from age 20y onwards were associated with increased LAVI in minimally adjusted models. Earlier age at first overweight was associated with increased LAVI in preliminary models.

When systolic function was examined it was found that increased BMI at age 26y was associated with poorer EF in fully adjusted models, while increased BMI at age 43y was associated with higher s' in preliminary models. Only EF had associations with overweight, with overweight at ages 26y and 36y associated with poorer systolic function on full

adjustment. Overall, associations between age at first overweight and EF or s' did not reach significance.

The trends of becoming overweight and obesity have reached epidemic proportions and are occurring at all ages including childhood and young adulthood.[20-23] Once weight is gained and individuals become overweight, it is very difficult to permanently return to a normal weight.[24] Therefore, determining the implications of long-term overweight on cardiac structure is important.

In the literature to date, there has been a focus on the cardiac effects of morbid obesity,[25, 26] and on those awaiting surgical interventions for morbid obesity, with post-gastroplasty weight loss being associated with better diastolic function.[17] However the effect of morbid obesity on LVM may not be the same as that of being slightly overweight. We have moved the focus away from morbid obesity in our work to look at the effects of unit increases in BMI and of the effect of being overweight (BMI >= 25 Kg/m^2). Our work tallies with cross sectional work showing that increased BMI is associated with diastolic dysfunction[27] and also agrees with work done by Arnlov et al who showed that greater BMI at an earlier age can predict worse diastolic function at a later age (at 50y and 70y respectively in his cohort).[28]

It was interesting to note that when BMI at 60-64y was added to models looking at the predictive power of earlier BMI on future diastolic function, greater BMI in the twenties seemed to be associated with a "protective" effect on future diastolic function. A similar reversal of association to a "protective" effect was also seen when BMI at age 60-64y was added to the age at first overweight-E/e' model, although this association was non-significant.

Reasons for these observations are speculative but it may be that this reversal of effect occurs because those with higher BMIs in their twenties have greater muscle mass rather than fat mass and that increased lean body mass is protective. Another explanation could be that the period between 20y-64y is a sensitive period for the relationship between BMI and diastolic function with change in BMI over this period being the determining factor on future diastolic function i.e. for a given BMI at age 20y, greater subsequent weight gain is associated with increased diastolic dysfunction. Of course, a third possible explanation is that this is an over-adjustment in the statistical models.

When BMI at age 60-64y was included in the age at first overweight models, the linear trend to worse diastolic function with earlier age at first overweight only remained for E/A. It is difficult to explain why this is, especially in light of the pseudonormalization issues known to be a problem with E/A. It is possible that BMI at age 60-64y may play a defining role in cardiac haemodynamics and accounting for it may allow E/A to reflect true diastolic function status. It may however also be the case, that including BMI at age 60-64y is an over-adjustment for the E/A models or it may be a chance finding. Another explanation could be that non-linear trends exist for the other measures in the final models, especially for those measures where the deviation from linear trend was significant.

Overall, when final adjustments were made by including BMI or overweight at 60-64y to the models, the associations at earlier ages in most cases became non-significant. This is likely to be due to tracking of BMI (and hence also of overweight) in the NSHD cohort[31] with individuals who had higher BMI in early adulthood having higher BMI throughout the 44y period of measurement [Table 7.5; initially shown in BMI-structure chapter (chapter 6), reprinted

below]. BMI at age 60-64y may be able to "capture" the previous BMI history and is thus significant in these models at the cost of previous BMI levels.

Table 7.5. Correlation between mean body mass indexes (combined for both sexes) at different ages.

	BMI at 60-64y	BMI at 53y	BMI at 43y	BMI at 36y	BMI at 26y	BMI at 20y
BMI at 60-64y	1.0000					
BMI at 53y	0.8607	1.0000				
BMI at 43y	0.7819	0.8530	1.0000			
BMI at 36y	0.7033	0.7680	0.8481	1.0000		
BMI at 26y	0.5475	0.6194	0.6924	0.7453	1.0000	
BMI at 20y	0.4461	0.5015	0.5727	0.6387	0.7781	1.0000

BMI – body mass index

It is therefore very difficult to separate effects of age at first overweight and current BMI (at age 60-64y). To be better able to answer this question, we would need to study general patterns of overweight across the life course including more trajectories where individuals are overweight in early life and become normal weight by 60-64 years. However, in the Medical Research Council National Survey of Health and Development, few people lost weight and or reduced weight categories i.e. from obese to overweight and overweight to

normal weight and previous analyses in our cohort have shown that such analyses lack power.[31]

The few studies that have attempted to quantify the effects of duration of obesity (increased duration of obesity associated with decreased EF but not with tissue Doppler markers of systolic or diastolic function) have included small numbers and have been based on recalled weights and hence the risk factor is prone to recall bias.[16, 18] While there has been inconsistent evidence in the literature on whether duration of obesity affects cardiac function,[19] our work shows that earlier age at first overweight is associated with poorer diastolic function but not with systolic function.

An important finding was that all the relations between BMI, overweight and age at first overweight all held on the inclusion of LVMI. This indicates that the deleterious effects of increased BMI and being overweight on future diastolic function were independent of diastolic dysfunction caused by a BMI-associated increase in LVMI described in earlier chapters.

While we showed consistent associations with diastolic function, BMI, overweight and age at first overweight were not consistently related to systolic function. This is in keeping with most recent work on the topic,[18, 19] although not so much with older work.[16, 17] Mechanistically, being overweight is more likely to affect cardiac haemodynamics through volume expansion, hypertension and increased cardiac output, alterations which in turn lead to diastolic rather than systolic dysfunction.[32-34] However, what was interesting to note

was that increased BMI and overweight at age 26y were both associated with worse EF in all models, including those with BMI/overweight at age 60-64y. It is difficult to say why BMI and overweight, at only age 26y, have this association – it may be a sensitive period – more work is needed to answer this.

Increased BMI at age 43y was associated with increased s' (i.e. better systolic function) in preliminary models and of all the overweight-s' models, those relating to overweight at age 43y were the closest to being significant. These results may indicate that BMI and overweight at age 43y is a sensitive period for s'. However, unlike EF, the s' associations indicate better systolic function with increased BMI. This may be an artefact or it may indicate that overall systolic function should not be estimated on the basis of one measure. Another explanation could be that the change in s' indicates a subtle change in long axis function (possibly an initial compensatory increase in systolic contractility) which cannot be captured by EF. It is also worth noting that the associations between EF and BMI/overweight at age 26y were not repeated for s'; this may reflect that BMI/overweight affect radial and longitudinal systolic contraction differently.

Strengths and limitations

Generalization to the UK population and the issue of missing data have been discussed in previous chapters. Strengths and limitations with regard to anthropometry and diastolic function measures have been discussed previously in the BMI-structure chapter (chapter 6) and in the methods chapter (chapter 3).

Echocardiography was only carried out in the last round of data collection. As such, with no baseline echocardiography, the possibility of diastolic dysfunction being a pre-existing diagnosis cannot be excluded. Reverse causality (prior diastolic dysfunction causing decreasing exercise capacity and increased BMI and overweight in the future) cannot be excluded.

Conclusions

Higher BMI and overweight from the age of 20y onwards is associated with poorer diastolic function at age 60-64y. The earlier the age at first overweight, the worse diastolic function is at age 60-64y. Current BMI/overweight accounts for most of the effects of previous BMI/overweight history on future diastolic function, although whether the effects of excess adiposity are reversible cannot be addressed by these data. Nevertheless these findings are consistent with an emphasis on weight reduction as early as possible in adult life to prevent a future deterioration in diastolic function.

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Chapter 8

Conclusion

In this thesis I have investigated the role of adult blood pressure (BP) and body mass index (BMI) histories over 28y and 44y periods of adult life respectively on cardiac structure and function at age 60-64y. I have shown that previous measures of BP provide additional information above and beyond current BP levels, for BMI the significance of earlier measures of BMI independent of current BMI is less clear cut but it is evident that earlier adiposity is associated with more adverse LV mass and diastolic function. I provide evidence that sensitive periods may exist when the impact of these RFs on cardiac structure and function is particularly marked and that rate of change in BP in midlife may adversely affect left ventricular (LV) mass (LVM) in later life. I have also shown that anti-hypertensive treatment (HTT) at various ages is associated with detrimental effects on cardiac structure, and function after accounting for differences in BP; I interpret that as probably reflecting a legacy effect of irreversible damage due to exposures occurring prior to the initiation of HTT.

In this chapter I will synthesize some of the common questions and themes that have arisen in the previous chapters. I will also comment on possible areas of future research.

An important finding in this work was that previous measures of BMI and BP were associated with current cardiac structure and function. While serial adjustments often attenuated, and by implication may therefore partially explain the effect of previous measures, previous high BP and elevated BMI were associated with adverse cardiac structure and function, even when additional RFs e.g. type 2 diabetes mellitus (T2DM) were included in the model. If elevated current RFs levels are taken to be representative of earlier elevated RFs levels these findings could be interpreted as providing support for earlier intervention to prevent later cardiac changes occurring. This cannot be definitively proved in the context of our study (i.e. it is not a randomized clinical trial looking at intervention), but at least for BP, our data suggest the timing of intervention during a sensitive period may be crucial given HTT was not associated with normalization of cardiac structure or function.

Overall, the similarity of the patterns of associations between BP and BMI at earlier ages and cardiac structure and function in the minimally adjusted models (increases in BP/BMI associated with detriments to cardiac structure and function) was striking. Studies examining epigenetic modifications and modification of cardiac myocyte structure and cardiac fibrosis might be informative on this issue.

Further research

Some areas of future research have already been highlighted earlier in this chapter and in the analysis chapters. Other areas of possible future research will be discussed in this section.

While we do not have BP measures prior to age 36y, we do have earlier BMI measures including anthropometric measures taken at birth. Investigating the influence of birth weight and childhood growth on these echocardiographic outcomes is an area for future research.

Electrocardiograms (ECGs) were recorded on study members during the last round of data collection and at immediately prior visits. We could correlate our echocardiographic LV hypertrophy (LVH) findings with electrocardiographically diagnosed LVH and also attempt to address the possibility of reverse causality using ECG-defined LVH at early time points. It would also be of interest to elucidate life course determinants of ECG-diagnosed LVH and its progression.

Pulse wave analysis, pulse wave velocity and carotid intima media thickness measures were also collected in the last round of data collection. These findings can be correlated with the echocardiographic findings to determine the role of central as opposed to brachial BP in cross-sectional analyses, and also to obtain a broader picture of the effect of adult life course RF history on the cardiovascular system as a whole.

Investigating the effect of duration of type 2 diabetes mellitus and incorporating measures of physical activity, diet and other measures of systolic function [as described in the methods chapter (chapter 3)] are planned to be carried out in the future.

Implications of the findings

Our findings demonstrate the importance of knowing previous BP and BMI histories and rate of change in BP even within the “normal” BP range. Developing a life course risk assessment approach for patients would be the logical extrapolation of our work. This would raise the

possibility of screening from very young ages allied to intervention in asymptomatic people. Both these measures would be controversial from the cost and risk-benefit points of view. Certain questions would need to be answered. We would need to qualify what is a "dangerous" or significant rise in the echocardiographic outcome measure and use that to determine what would constitute a "dangerous" rise in longitudinal BP or BMI measures. We would also need to determine how frequently patients would need to be screened (especially those who are asymptomatic and with "normal" BP and BMI levels) to pick up "dangerous" rises in RF levels. Ultimately, we would need to relate life course RF measurements to hard cardiovascular end points (e.g. death, myocardial infarction, stroke and heart failure). A comparison of current risk assessment practice against a life course approach to risk determination using a randomised clinical trial (RCT) is required. However, achieving hard end points in a randomised clinical trial would be difficult with a life course methodology, as by definition, "life course" covers a substantial period of time. Softer end points, which are independently associated with cardiovascular morbidity and mortality (such as those we have used e.g. LVH and E/e') may need to be used to enable a shorter length of study. It would be possible to carry out an RCT using life course methodology if the study population were elderly and had detailed past medical records. However, the older the participants, the less the likelihood of availability of detailed records from early life.

A variety of other measures of physical function (grip strength, balance tests, bone densitometry etc.), mental health (cognitive function tests etc.), genetics (telomere length measurement), lung function and a variety of blood tests (kidney function, coagulation, hormone levels) have been assessed in the last round of data collection, with some of these tests having also been conducted in previous rounds. Integrating our findings with the results

of these other tests will give an in-depth and broad-spanning picture of life course determinants of both healthy and unhealthy ageing and help to identify possible common aetiological/mechanistic pathways and targets of correctly-timed intervention.

Future rounds of research where we look again at the cardiac structure and function of study members would be warranted. Harder end-points (as discussed above) would be more prevalent and would, for example, allow a better understanding of the seriousness of having a fast rising BP at a young age.

Our work has provided a number of interesting new findings and using a similar approach to other RFs and echocardiographic outcomes in our study will provide further information about the life course effects of RFs on cardiac structure and function. The more widespread the adoption of the life course approach in Cardiology, the better understanding we will get of earlier-life risk factors and how to intervene more effectively at an earlier stage of disease.