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A Life Course Approach to Cardiovascular Ageing



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Although cardiovascular disease (CVD) is rare until middle age, it has long been known that the pathophysiological process of atherosclerosis, which ultimately results in disease, is initiated in childhood. In order to identify points of intervention early in the disease development process, well before the clinical manifestation of disease, it is important to understand age-related change in key CV risk factors, such as blood pressure (BP), and to identify exposures across life, which influence disease development. A life course approach provides a framework in which to do this.

Life Course Epidemiology

A life course approach in epidemiology investigates the biological, behavioural and social pathways that link physical and social exposures and experiences during gestation, childhood, adolescence and adult life, and across generations, to later life health, disease risk and ageing (Kuh and Ben-Shlomo 2004). Pioneering studies by David Barker in the 1980s, which related low birth weight as a proxy marker of poor growth and nutrition in utero to increased rates of CHD, led to the development of the fetal programming or "Barker" hypothesis (Barker 1998). This hypothesis states that exposures during critical developmental periods have long-term consequences for chronic disease. Life course epidemiology emphasises the importance of early social, as well as biological, exposures. The impact of early life socioeconomic conditions on adult health was initially seen as a competing model to the fetal programming hypothesis. Life course epidemiology also acknowledges the importance of adult lifestyle and risk factors, such as hypertension and inactivity, but recognises their tracking from childhood to adulthood. The life course perspective as outlined by Kuh and Ben-Shlomo thus integrated and extended these three apparently conflicting theories of disease aetiology; fetal programming, social causation and adult lifestyle.

More recently, the importance of age-related change in functional capability, measured with tests of muscle strength and physical performance (such as grip strength and walking speed) and cognitive performance, has been highlighted (Kuh et al. 2014). Functional capability, and the physiological systems (including the CV system) on which they depend, exhibit age-related change across the whole of life. With regards to CV ageing, and rather than simply focusing on disease, measures of cardiometabolic function, such as BP, lipids, and glucose and insulin, allow the full spectrum of function from high to low, to be investigated. Understanding how these markers change across life, identifying underlying 'normal' or 'healthy' trajectories, and the risk factors associated with deviation from these trajectories, are potentially important for fully understanding the development of CVD (Lawlor and Hardy 2014).

Life Course Studies and the MRC National Survey of Health and Development

A life course study may be described as a cohort study that has information from at least one stage of development (gestation, childhood or adolescence) and in adult life. This distinguishes it from a general cohort or longitudinal study, where individuals may be followed up repeatedly, but over a shorter period of life. The ideal study design for research taking a life course approach is a birth cohort, which follows the same individuals from birth (or pregnancy or even pre-conception). The oldest such cohorts, for example the Medical Research Council (MRC) National Survey of Health and Development (NSHD), are only just now entering older age.

The NSHD, housed in the MRC Unit for Lifelong Health and Ageing at UCL, is based on a nationally representative sample of 5 362 births that took place in one week in March 1946 in England, Scotland and Wales (Wadsworth et al. 2006). The study has a wealth of prospective information collected at all stages of life on body size, cognitive tests, and socioeconomic, psychological and lifestyle characteristics. At ages 36, 43 and 53, study members were interviewed in their own homes by a team of trained research nurses, allowing measurements of BP, lung

function and cognition to be made. Between 2006 and 2010, when the cohort were aged 60–64, participants were invited to attend one of six clinical research facilities. Detailed vascular measures, such as carotid intima-media thickness (cIMT) and pulse wave velocity (PWV), were undertaken, and measures of cardiac structure and function were obtained through echocardiography (Kuh et al. 2011).

We highlight examples of research from NSHD to illustrate how a cohort study can be used to provide novel insights into CV ageing. First we outline research on BP trajectories, and second describe research relating two life course exposures, body size and socioeconomic conditions, to C V o outcomes.

Life Course Trajectories of Blood Pressure

Even with a measure as common as BP, there is still no single study with BP measured on the same individuals across the whole of life. An improvement over cross-sectional analyses of individuals of different ages, is to compare multiple longitudinal cohorts with repeated measurements that cover different periods of life. We used information on systolic BP (SBP) from seven UK prospective cohort studies, including the NSHD, each with BP measures covering different but overlapping periods of life from 7 to 80+ years (Wills et al. 2011). Four life course phases of SBP change were identified: a rapid increase coinciding with peak adolescent growth; a more gentle increase in early adulthood; a midlife acceleration beginning in the fourth decade; a deceleration in late adulthood where increases in SBP slowed and at very old age declined. The extent to which the slowing of the increase, or even decrease, in BP is driven by the survival of those who are most healthy, with lower BP, and less prone to premature mortality, or by effective BP lowering treatment, remains unclear. The decline was less evident in analyses excluding individuals on antihypertensive medication, suggesting treatment may play a role. But age-related weight loss, arterial stiffening and changes in the autonomic control of blood pressure are possible age-related processes, which could explain a decline (Reitz and Luchsinger 2007). An occupational, and thus more healthy, cohort exhibited a SBP trajectory, which did not begin the accelerated rise until a later age when compared with the general population cohorts. This variation, together with evidence of less pronounced age-related rises in studies from non-industrialised farming populations, suggests the rise in BP is not necessarily part of the physiological ageing process, but is rather a result of western lifestyles.

Evidence is accumulating to suggest that the accelerated midlife rise in BP has implications for subsequent disease development. In NSHD adults belonging to a subgroup with more marked increases in midlife BP were more likely to have undiagnosed angina than other participants (Wills et al. 2012). Greater midlife increases in SBP were also associated with poorer cardiac structure at age 60–64 years (ghosh et al. 2014). greater BP increase between 43 and 53 years was a stronger risk factor of higher left ventricular mass index than more recent BP increase. Whether this finding represents a detrimental impact of rate of increase during a particularly sensitive period of adult life, or whether there is a lag effect which is independent of age, or is a result of reverse causality, remains to be seen. These findings raise the possibility, which should be investigated further, of identifying those at risk of future disease according to their rate of change in BP, rather than through a single measurement with a threshold for hypertension.

Life Course Factors Associated with CV Ageing: Examples

Developmental Origins of CVD

Since David Barker's original work, many studies have investigated the relationship between birth weight and CVD. Systematic review of the existing literature has found consistent association of lower birth weight with increasing rates of CHD (Huxley et al. 2007), and of lower birth weight and higher BP in adulthood (Huxley et al. 2002). There is only weak evidence of an association between birth weight and lipids (Huxley et al. 2004). Comparisons of multiple studies with BP measured at different ages suggested that the negative association between birth weight and BP, although initiated in utero, was amplified with age (Law et al. 1993). However, this might be a result of stronger associations in historical, compared to more contemporary, birth cohorts. The idea of amplification is equivalent to hypothesising that those of lower birth weight have faster increases in BP than others. Using the repeated measures of BP in NSHD suggested that birth weight was associated with the level of BP in early midlife, but inconsistent with amplification, not with the rate of BP increase (Hardy et al. 2003). It should be noted that birth weight has been the most commonly used proxy marker of fetal growth, largely because it is widely available in historical studies. Contemporary cohort studies have collected more sophisticated measures of fetal growth through pregnancy, which should provide new insights into mechanisms, but such cohorts are still young in terms of disease progression.

Life Course Body Size

High body mass index (BMI) in late childhood and adolescence is associated with a higher risk of CHD, but there is less and somewhat conflicting evidence in relation to BMI in early childhood (Owen et al. 2009). The strength and direction of association may thus change with age at BMI measurement. Utilising the unique repeated measures of height and weight in infancy, childhood, adolescence and adulthood in NSHD, high weight in infancy was found to be protective, and fast increases in BMI during the pubertal period detrimental, for adult BP (Hardy et al. 2004). greater gains in BMI in early adulthood were related to a worse adult lipid profile (Skidmore et al. 2007). A greater accumulation of time spent overweight during adult life was related to higher midlife BP (Wills et al. 2010), and to higher cIMT in early old age (Charakida et al. 2014). Importantly, in relation to cIMT, findings suggested that as well as delaying becoming overweight, loss of weight at any point in adulthood, even if temporary, may be beneficial to vascular health.

It is not just adiposity that is important for CV ageing, as shorter adult height is associated with higher rates of CHD (Paajanen et al. 2010). Adult height, and in particular leg length, can be considered as a biomarker of early life environmental factors reflecting pre-pubertal growth. This was highlighted in NSHD, where leg length was more strongly related than trunk length to breastfeeding and higher energy diets in early childhood, and more advantaged early life socioeconomic environment (Wadsworth et al. 2002). In subsequent analysis, shorter leg length was related to both BP level and faster age-related increases in BP (Langenberg et al. 2005). This may suggest that detrimental early life influences on vascular structure and function may increase vulnerability to the effects of ageing on the arterial tree. We have also demonstrated that taller height in early childhood was related to better adult lipid levels (Skidmore et al. 2007) and cIMT (Johnson et al. 2014).

Life Course Social Inequalities

Socioeconomic position (SEP) in childhood, as indicated by the father's occupational social class, education, income or living conditions, has been shown in a multitude of studies to be associated with CHD (Galobardes et al. 2006) over and above the influence of adult SEP. In the NSHD, disadvantaged childhood SEP was associated with both higher BP at age 36 and with a faster subsequent rate of increase in BP, such that the association was stronger by age 53 (Hardy et al. 2003). Such amplification with age could explain why little association has been found in other studies between childhood SEP and BP measured in childhood and early adulthood, but associations between childhood SEP and adult BP have been found. In further NSHD research relating childhood and adult SEP to adult cardio-metabolic outcomes, disadvantaged SEP in childhood was found to be particularly important for men, more important than later life SEP, suggesting a sensitive period for exposure in earlier life (Murray et al. 2011). In contrast, for women, accumulation of socioeconomic disadvantage over the whole life course predicted poorer cardio-metabolic health.

Conclusion

Evidence from the NSHD and other longitudinal studies suggests that changes in cardiovascular function start early in life, well before the manifestation of disease, and that early life risk factors are involved in initiation of adverse functional change. Understanding the development and progression of disease across the life course is vital to identify potential early interventions to prevent CVD.

Key Points

- Life course epidemiology provides a framework in which to study cardiovascular ageing across the life course.
- Data from longitudinal cohorts studies following the same individuals throughout life are required to study cardiovascular ageing from a life course perspective.
- Understanding how markers of cardio-metabolic function (such as blood pressure, lipids and glucose and insulin intolerance) change across life and the characteristics associated with deviation 'normal' age-related change is key to fully understanding disease development
- Changes in blood pressure in midlife are increasingly being found to be associated with CVD progression and outcomes
- Factors from across life influence CV ageing; pre-natal and postnatal growth are associated with later CVD and cardio-metabolic risk factor trajectories, and social inequalities in CVD risk are initiated in childhood

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