Life-course influences on occurrence and outcome for stroke and coronary heart disease
To Hilma, Lova, Gustav

and all children

“Old age is like everything else. To make a success of it, you’ve got to start young.”

Theodore Roosevelt 1858-1919
Cecilia Bergh

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Abstract


Although typical clinical onset does not occur until adulthood, cardiovascular disease (CVD) may have a long natural history with accumulation of risks beginning in early life and continuing through childhood and into adolescence and adulthood. Therefore, it is important to adopt a life-course approach to explore accumulation of risks, as well as identifying age-defined windows of susceptibility, from early life to disease onset. This thesis examines characteristics in adolescence and adulthood linked with subsequent risk of CVD. One area is concerned with physical and psychological characteristics in adolescence, which reflects inherited and acquired elements from childhood, and their association with occurrence and outcome of subsequent stroke and coronary heart disease many years later. The second area focuses on severe infections and subsequent delayed risk of CVD. Data from several Swedish registers were used to provide information on a general population-based cohort of men. Some 284,198 males, born in Sweden from 1952 to 1956 and included in the Swedish Military Conscription Register, form the basis of the study cohort for this thesis. Our results indicate that characteristics already present in adolescence may have an important role in determining long-term cardiovascular health. Stress resilience in adolescence was associated with an increased risk of stroke and CHD, working in part through other CVD factors, in particular physical fitness. Stress resilience, unhealthy BMI and elevated blood pressure in adolescence were also associated with aspects of stroke severity among survivors of a first stroke. We demonstrated an association for severe infections (hospital admission for sepsis and pneumonia) in adulthood with subsequent delayed risk of CVD, independent of risk factors from adolescence. Persistent systemic inflammatory activity which could follow infection, and that might persist long after infections resolve, represents a possible mechanism. Interventions to protect against CVD should begin by adolescence; and there may be a period of heightened susceptibility in the years following severe infection when additional monitoring and interventions for CVD may be of value.

Keywords: cardiovascular disease, stroke, risk factors, adolescence, stress resilience, adult infections, life-course epidemiology, cohort study

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# Table of Contents

LIST OF PUBLICATIONS ........................................................................................................ 9

ABBREVIATIONS .................................................................................................................. 10

INTRODUCTION .................................................................................................................... 11
A life-course approach to stroke and coronary heart disease ............................................. 12
Life-course conceptual models ............................................................................................. 13
Early life exposures and adult cardiovascular disease ....................................................... 14
Early stress and adult health and resilience ........................................................................ 15
Stress and coping .................................................................................................................. 16
The Hypothalamic-Pituitary-Adrenal (HPA) axis and the stress response .......................... 17
Adolescence as a period of transition ................................................................................... 18
Risk factors from across the life-course for stroke and coronary heart disease ............... 19
Psychosocial stress and stress resilience in adolescence .................................................... 19
Physical fitness and developmental characteristics in adolescence ............................... 20
Infections and cardiovascular disease ................................................................................ 21

SUMMARY ............................................................................................................................ 24

AIMS ...................................................................................................................................... 25

MATERIAL AND METHODS ............................................................................................... 26
Study population – a conscription cohort ............................................................................ 26
Measures ................................................................................................................................ 26
Stress resilience .................................................................................................................... 26
Cognitive function ................................................................................................................ 28
Physical fitness and anthropometrics ................................................................................ 29
Health status ........................................................................................................................ 29
Infections ............................................................................................................................... 30
Socioeconomic characteristics ............................................................................................ 31
Outcomes ............................................................................................................................... 31
Stroke .................................................................................................................................... 32
Coronary heart disease ......................................................................................................... 32
All-cause cardiovascular disease ....................................................................................... 32
Exclusions for papers I-IV .................................................................................................... 32
Statistical analysis ................................................................................................................. 33
Ethical considerations .......................................................................................................... 36
LIST OF PUBLICATIONS

This doctoral thesis is based on the following original papers, which are referred to in the text by their Roman numerals:


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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<td>CHD</td>
<td>Coronary heart disease</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DALYs</td>
<td>Disability-adjusted life-years</td>
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<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<td>EVF</td>
<td>Erythrocyte volume fraction</td>
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<tr>
<td>HPA axis</td>
<td>Hypothalamic-pituitary-adrenal axis</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>LRT</td>
<td>Likelihood ratio test</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<tr>
<td>SEI</td>
<td>Socioeconomic index</td>
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<tr>
<td>SNS</td>
<td>Sympathetic nervous system</td>
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<tr>
<td>SAH</td>
<td>Subarachnoid haemorrhage</td>
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<td>WHO</td>
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INTRODUCTION

This thesis examines characteristics in adolescence and adulthood linked with subsequent cerebrovascular (stroke) and cardiovascular (CVD) risk. One area is concerned with physical and psychological characteristics in adolescence, which reflects inherited and acquired elements from childhood, and their association with occurrence and outcome of subsequent stroke and coronary heart disease (CHD) many years later. Adolescence is described as a developmental stage central for reaching our ‘optimal’ health potential. The second area focuses on severe infections in adulthood and risk of CVD.

Cardiovascular disease, including stroke and CHD, remains a leading cause of death and disability among both men and women globally. Worldwide, these diseases are currently responsible for approximately 17.3 million of the 56 million total deaths per year, and their consequences are associated with a huge burden of economic cost and individual suffering. Stroke is the most common cause of serious, long-term, neurological disability in adults in industrialised countries, and it is the single somatic disease that accounts for the largest number of admissions in Swedish hospitals. Globally, stroke is the second leading cause of disability-adjusted life-years (DALYs). The absolute number of people who have a stroke annually, and the number with related deaths and DALYs lost, is increasing.

Stroke was traditionally thought of as a disease of elderly people. However, there is some evidence of an increasing stroke incidence in early middle age. Although age-adjusted mortality and age-standardized rates of stroke have decreased, no such trend has been observed for early stroke, before the age of 65 years. Moreover, the proportion of stroke burden is greater overall in younger individuals, and risk of stroke recurrence in patients whose first stroke occurred before age 55 years remains substantially increased for decades subsequently. As the cardiovascular and stroke-related burden is substantial, it is of importance to identify potentially modifiable risk factors, not only for prevention of disease onset, but also for prevention of a poor prognosis and outcome. Understanding a disease means being able to explain its clinical and preclinical manifestations in terms of biological mechanisms and pathways, from early life and
onwards. This thesis uses a life-course approach to examine risks for CVD where exposures significantly pre-date disease onset.

A life-course approach to stroke and coronary heart disease

Until relatively recently, most of our knowledge concerning the aetiology of CVD focused on risk factors acting in adult life such as diet, smoking, physical activity, hypertension, and adult obesity. The INTERSTROKE and INTERHEART studies, investigating risk factors from across different regions and populations worldwide, suggest that ten established major risk factors account for approximately 90% of the population attributable risk for stroke and CHD. These modifiable risks are becoming more and more established. Behavioural, metabolic and environmental modifiable risk factors do not only account for disease risk, but also for more than 90% of the stroke burden as measured in DALYs.

There may be foetal and other early life influences on stroke and CHD risk. In the 1970s, Forsdahl investigated the role of poor living conditions during childhood in Norway to explain a higher risk of later CVD. Barker’s research on foetal exposures from the 1980s and onwards proposed that stroke and CHD originate from foetal life and infancy. The associations found with low birthweight and CHD was proposed to be explained by developmental plasticity and compensatory growth.

There is further evidence that the pathophysiological process of atherosclerosis, whereby arteries become narrowed and damaged by deposition of fatty material, which ultimately leads to CHD and ischemic strokes, begins in childhood and young adulthood. Cardiovascular risk factors, such as high blood pressure, obesity, dyslipidaemia, and insulin resistance are present in childhood, associated with atherosclerosis and endothelial dysfunction and track into adulthood. CVD may therefore have a long natural history with accumulation of risks beginning in utero and continuing through childhood, adolescence and adulthood, although typical clinical onset does not occur until later in adulthood. For this reason it is important to adopt a life-course approach to understand accumulation of risks, as well as identifying age-defined windows of risk, from early life to disease onset.
Life-course conceptual models

Life-course epidemiology is the study of exposures and pathways that influence health and development over time in individuals. Exposures and characteristics can have delayed consequences, including long-term behavioural, psychosocial and biological processes that link health and disease risk through exposures acting during gestation, childhood, adolescence, or in adult life. Life-course studies demonstrate that an individual’s health is the result of complex mechanisms combing genetics, lifestyle, and the social and psychological environment acting from the youngest age. The prenatal period, childhood and adolescence appear to be important phases of human development for shaping the basis for later health.

The critical/sensitive period model suggests that during a phase of rapid development or growth, a biological system is more sensitive to environmental exposures and to deviations from expected experiences – particularly in utero and early life. This model hypothesises that environmental exposures may do more damage to body systems at these developmental stages than at other times, with lasting effects that are not modified in any dramatic way by later experience. This process precipitates the development of chronic disease in later life. Plasticity, however, is present across the life-course.

Another model hypothesises that risk factors for chronic disease often cluster together because many are related to socioeconomic position or other forms of persistent disadvantage. The pathways model (or chain or risk model) proposes that certain events occurring earlier in life may have pathway effects by setting a group of individuals in a particular life trajectory, influencing later opportunities, and exposures to health risk factors. These “ongoing social processes” or “chain of risk”, explain how an exposure will lead to another and have an impact on body functions increasing disease risk.

The accumulation of risk model proposes that long-term exposures across the life course can accumulate and have consequences on health. When risk factors gradually accumulate over the life-course, or part of the life-course, this does not preclude that factors acting at sensitive developmental periods have a greater impact. As the number, duration, and severity of exposure increase, there is cumulative damage to biological systems. Risk exposures may be independent or clustered. Critical/sensitive periods, pathways and accumulation models are not mutually exclusive and may operate simultaneously.
Early life exposures and adult cardiovascular disease

One of the first applications of life-course epidemiology was in cardiovascular disease research, but is now seen to be relevant for a broader range of diseases. The interest in early life factors stemmed from the need to understand the natural history of adult risk factors, and from the inability of the lifestyle model to explain social and geographical variations in chronic disease risk. The research on prenatal and early life exposures as origins of adult health was, as previously mentioned, stimulated by findings that the process of CVD begins in utero and early life.\textsuperscript{21, 25} This line of research linked poor childhood living conditions\textsuperscript{20} and impaired early development\textsuperscript{21, 39, 40} to adult cardiovascular disease. Growth in utero was associated with blood pressure in childhood and adulthood, and mortality from CVD.\textsuperscript{41} Barker’s hypothesis on the foetal origins of CVD was presented as a direct challenge to the adult lifestyle model of chronic disease. However, the lifestyle model, which arose from the study of those in mid-life, has gradually extended beyond adulthood as it was increasingly recognized that established classic risk factors could begin in childhood. Life-long smoking, dietary, and exercise habits are acquired in childhood and adolescence; but often track to adult life.\textsuperscript{42}

Studies of markers of socioeconomic circumstances in relation to cardiovascular disease found an effect that was additional to the effect of adult risk factors and socioeconomic conditions, these studies suggest that socially patterned exposures in childhood have important influences on adult health.\textsuperscript{43} Environmental conditions and experiences during prenatal life, infancy, childhood and adolescence are associated with illness and poor early growth, which make individuals more susceptible to developing adult chronic disease, either independently, or in combination with adult risk factors. Most of the environmental exposures are also socially patterned. Studies of socioeconomic circumstances over the life course have shown associations with stroke and CHD risk. Stroke risk is particularly associated with parental, hence, childhood, socioeconomic position.\textsuperscript{44} These studies suggest that both early and later environmental conditions may have independent influences on the risk of stroke and CHD in adult life. The accumulation of –and interaction between- influences acting at different stages of life helps determine socioeconomic patterns of CVD within and between populations. This has stimulated further research into other adult risk factors to do with the psychosocial environment and
childhood risk factors.\textsuperscript{16, 45} One hypothesized mechanism linking early life and later disease relates to the biology of stress.

**Early stress and adult health and resilience**

Psychological stress is a state of the mind, involving brain and body as well as their interactions. The brain is the central organ of stress and adaptation to stressors because it perceives what is potentially threatening and determines the behavioural and physiological response.\textsuperscript{46} Chronic psychosocial stress and consequent physiological dysregulations, as well as individual health behaviours, are viewed as catalysts of accelerated disease trajectories.

Childhood is thought to be a crucial period of development for the stress response, and experiences in childhood may make a child more or less susceptible for future stress. Being exposed to adverse circumstances like material deprivation, social conflict, lack of social support, trauma or abuse appear to alter stress response systems, and one area of influence is on the Hypothalamic-Pituitary-Adrenal (HPA) axis, the central nervous system (CNS), the autonomic nervous system (ANS), and the sympathetic system (SNS).\textsuperscript{47-49} Low socioeconomic position increases the likelihood of stressors in the home and neighbourhood.\textsuperscript{50, 51}

Early life is recognized as a window of vulnerability, but also of opportunity. Individual differences in the brain’s interpretation of and the body’s reaction to environmental stressors are determinants of either vulnerability towards or resilience against stress-related diseases.\textsuperscript{52} Resilience refers to a dynamic process of positive adaptation in the face of stress and adversity or the ability of an organism to withstand threats to stability in the environment.\textsuperscript{46, 53-55} In a sense, resilience represents the ability to bend without breaking in the face of environmental or psychological perturbations, and it can involve an active resistance to adversity through coping mechanisms that operate at the time of trauma.\textsuperscript{56} Individual differences in constitutional (genetics, development, experience), behavioural (coping and health habits), and historical (trauma/abuse, major life events, stressful environments) are factors that might determine one’s resilience to stress.\textsuperscript{57} The individual traits that allow for more flexible outcomes depend upon genetic influences and experiences, particularly in early life. Adverse childhood experiences have a powerful role and can alter resilience in individuals, making it more difficult for them to respond normally to ad-
verse situations in adulthood.\textsuperscript{54} In contrast, there are also studies suggesting that being exposed to adverse situations during early life can in fact increase resilience to stress.\textsuperscript{58} A loving, healthy and supportive childhood environment, avoiding unmanageable stress, but offering chances to embrace and conquer life challenges, can support resilience building from an early age.\textsuperscript{55}

**Stress and coping**

One definition of stress relates to the imbalance between the perceived demands placed on an individual and the ability to meet those demands.\textsuperscript{59} Psychosocial stress therefore occurs when an individual feels that environmental demands tax or exceed the adaptive capacity, resulting in psychological and biological changes, which in some circumstances may place him or her at higher risk of disease.\textsuperscript{60} Stress can occur whenever either the real or the perceived demands exceed either real or perceived capacity to cope. However, individuals differ as to which events or demands they find stressful and in what way they respond to them. This perspective has led to the study of coping and to the development of techniques aimed at helping individuals to overcome stress by increasing the effectiveness of their coping strategies. Coping, using behavioural or psychological techniques utilized to overcome stress, has been linked to resilience in individuals.\textsuperscript{61}

Coping is intimately related to the concept of cognitive appraisal, and most approaches in coping research follow Folkman and Lazarus,\textsuperscript{59} who define coping as “the cognitive and behavioural efforts made to master, tolerate, or reduce external and internal demands and conflicts among them”. Cognitive processes, personality traits, and active coping mechanisms contribute to resilience. These qualities also interact with biological factors to enhance adaptation in the face and aftermath of traumatic events, and confer resilience.\textsuperscript{62} Characteristics such as high level of intellectual functioning, efficient self-regulation, active coping styles, optimism and secure attachment were observed in youth who had faced adverse situations and settings, and yet did not succumb to the adverse impact of extreme stress.\textsuperscript{63}
The Hypothalamic-Pituitary-Adrenal (HPA) axis and the stress response

From a physiological perspective, when the brain detects a threat, a coordinated response involving autonomic, neuroendocrine, metabolic and immune components is activated. A key system in the stress response that has been extensively studied is the HPA axis. Activation of the HPA axis is necessary to meet and adapt to the environment, and the secretion of glucocorticoids mobilizes energy necessary for fight-or-flight responses. However, when the HPA axis is continuously activated, during chronic stress, it may accelerate the pathophysiological process. The HPA axis is involved in restoring homeostasis and subsequent adaptation to perceived stress. Therefore, the activation of the HPA axis plays a pivotal role in the stress response. While short-term activation allows for adaptive changes to the challenge, in the long-term this can be deleterious for the organism. It is hypothesized that the stress-related system was not designed to be constantly activated. Overuse may contribute to the breakdown of many biological systems. In particular chronic exposure to stressors occurring during periods of maturation (perinatal, adolescence) appear to have strong long-term effects on subsequent behavioural and neuroendocrine response to stressors.

The HPA axis is not fully mature at birth and shows important developmental changes throughout childhood, in both basal activity and endocrine reactivity. There is evidence, mostly from animal models, that important parameters of the physiological response to stress are set in early life and poor control of the stress response due to these early life exposures can persist across life. Early life exposure to adverse childhood experiences, like trauma, abuse or maltreatment, has been linked to alterations in brain structure and neurobiological stress-response systems. Several studies have suggested that exposure to chronic stress during sensitive periods of development may alter the balance and responsiveness of physiological systems and have long-term effects of health. Stress dysregulation during sensitive periods in brain development and maturation can result in future sensitivity, and is associated with an increased disease risk.

There is growing evidence that several hormonal axes, such as the HPA axis, are more plastic in early life, but later more intense exposures can influence too. Animal studies have suggested that early-life stress can alter HPA axis function in a way that can persist over the life course.
Therefore, the continued ability across life to respond appropriately to stress is a necessary component in disease prevention. Maladaptation to chronic stress will likely make an individual with low stress resilience more vulnerable to some diseases, including cardiovascular disease, through an effect of the HPA axis and the sympathetic nervous system which can result in inflammation and altered metabolic and cardiac autonomic control (biological pathways). 78 Other relevant stress-related mechanisms might work through behavioural pathways and lifestyle factors, such as physical activity patterns, diet habits, alcohol consumption and smoking.

Adolescence as a period of transition
Adolescence occurs between the ages of 10 and 19 years. 79 It is a critical/sensitive period associated with physiological, psychological, personality and identity development, 79, 80 and as such a time when crucial transitions to adulthood take place. Childhood and adolescent growth and development set the scene for future mental and physical health as well as adult behaviours. 81, 82 During this period, a number of experiences occur at specific times to attain an ‘optimal’ brain development. 80 The brain architecture is highly sensitive to environmental influences during early life, affecting health at this period, and over subsequent life.

Adolescence represents a particularly important life stage for health-related behavioural development. 83 It is a time when risks accumulated since childhood can start to affect the behaviour of young people and influence their transition to adulthood. Health behaviour established in childhood and adolescence often tracks into adulthood. Some behaviour, like smoking, is addictive and tracks strongly into adult life. 84, 85 Others, such as physical activity and body mass index, BMI, demonstrate more moderate levels of tracking. 86-88 Adolescence is the time of life when mental health can begin to be a problem for some young people.

Within a life-course perspective, adolescence represents a critical phase in life for achieving human potential. Adolescence is characterized by: 1) dynamic brain development (a critical/sensitive period); 2) interaction with the social environment that shapes development and health behaviours that will continue the same pathway or trajectory as established in childhood, or that will be transformed in significant ways (pathways model); 3)
CECILIA BERGH  Life-course influences on occurrence of stroke and CHD  19

the beginning/continuation of a (potential) gradual accumulation of risk that might continue over the life-course (accumulation of risk model).

Risk factors from across the life-course for stroke and coronary heart disease

As recent evidence suggests that factors acting across the life-course, rather than just adulthood, are important in determining the risk of cardio-vascular disease, life-course influences has become a useful field to further explore aetiological processes and pathways of risk accumulation. Therefore, individual psychological, physical and medical characteristics in late adolescence, and later adulthood, are possible modifiable targets for subsequent disease burden in the general population. The possibility of detecting markers of an increased risk of stroke and CHD offers an opportunity to target interventions more efficiently.

Psychosocial stress and stress resilience in adolescence

Recent evidence has indicated that psychosocial stress is a possible risk factor for stroke and CHD, adding to known and potentially modifiable established risk factors. Psychosocial is defined here as “the interaction between people and their social environment involving psychological processes”. Recognised modifiable CVD risk factors include high blood pressure, atrial fibrillation, hypercholesterolemia, diabetes, obesity, smoking, alcohol consumption and physical inactivity, but further environmental factors, as well as inherited or acquired health conditions, are likely to be relevant to disease risk.

It has been suggested that exposure to psychosocial stress, through its influence on metabolic and behavioural pathways, is associated with a variety of adverse health outcomes, including stroke and CHD. However, the evidence to date is inconclusive. There have been potential methodological concerns in some studies making clear causal inference difficult, including problems of reporting bias due to the use of retrospectively collected information. Short duration of follow up is unlikely to capture significant chronic accumulation of risk relevant to the long natural history of CVD. It is also possible that stressful exposures in middle age are confounded by other previously accumulated cardiovascular risks. These risks are probably not independent from each other; therefore, stress might be working through other risks. A further issue is that there
are between-individual differences in what constitutes stressful exposures and the ability to cope with them. A measure of stress resilience, or the ability to cope with stress, from adolescence, measured long before the onset of stroke and CHD, could provide an opportunity to explore disease susceptibility relevant to chronic stress. Individuals with low stress resilience are likely to have a poorly controlled stress response and less efficient coping strategies to stress and adversity in daily life. The activation of the HPA axis response in those individuals could result in an overexposure to stress hormones, increasing the possible long-term consequences of exposure to stress.

**Physical fitness and developmental characteristics in adolescence**

Identifying the behavioural and other pathways linking psychosocial stress and stress resilience to stroke and CHD provide a key to understanding mechanisms that can be tackled to reduce CVD risk. Social and material circumstances across the life course are associated with CHD and stroke risk although the mechanisms explaining this are incompletely understood. Several indicators of early life socioeconomic disadvantage – low birth weight, short stature, household crowding, and low paternal social class – have been shown to have strong links with stroke and CHD.44, 99, 100 The effect of socioeconomic circumstances may accumulate across life with poorer circumstances at any point in life likely to be detrimental for subsequent physical and mental capability and therefore increase subsequent disease risk.

It is well known that higher level education confers protection against CVD, possibly involving pathways through cognitive and non-cognitive psychological factors as well as physical fitness and other aspects of health behaviour. Stroke and CHD are associated with circumstances in childhood, such as socioeconomic position;99 with height as a marker of early development,101 as well as exposure to stress;102 and also with cognition.103-105 Cognition is an important determinant of educational achievement and a strong marker of development and future health, but also related to health behaviour. It is likely that cognitive function in adolescence is associated with health risk behaviour from teenage to later in life.80

Childhood and adult physical fitness and development are powerful markers of future health and CVD risk.106-111 Physical fitness describes a set of physiological attributes that person has or achieves, which confer
the ability to perform physical activities without under fatigue. Physical fitness is mainly determined by physical activity patterns over a prolonged period of time, but genetics can also contribute to individual variations.\textsuperscript{112, 113} The health-related components of physical fitness include cardiorespiratory fitness, body composition and musculoskeletal function.\textsuperscript{114} Cardiorespiratory fitness is the ability to transport and use oxygen and is usually expressed as maximal oxygen uptake (VO\textsubscript{2} max). Cardiorespiratory fitness enhances ‘endurance’, that is the ability to perform physical activity for an extended period. Existing evidence from observational studies demonstrates that factors from early life onwards are associated with physical capability in later life and that the influence of many of these factors in cumulative. Adverse socioeconomic circumstances in childhood are associated with lower physical capability in adulthood.\textsuperscript{115} Life-long patterns of physical fitness are developed during adolescence but are influenced by experiences in childhood.\textsuperscript{79, 86, 87}

From a life-course perspective, health risk behaviour tends to cluster; an individual who is a smoker is likely to also engage in unhealthy patterns of alcohol consumption, and have a sedentary and stressful lifestyle. It is also well established that health behaviour is influenced by characteristics signalled by socioeconomic group. To examine the extent to which behavioural factors associated with stress resilience are of importance for CHD and stroke, these can be examined as potential mediators in pathways from stress resilience to cardiovascular outcomes. This will help determine whether the most useful intervention target is stress (or stress resilience) itself, or related phenomena such as fitness and behaviour.

**Infections and cardiovascular disease**

In adulthood, there may also be exposures that have delayed influence on the occurrence of CVD, for example infectious disease also plays a role in shaping CVD risk.\textsuperscript{89} Previous studies have shown that approximately one third of diagnoses of ischemic stroke in children and younger adults are associated with recent infection. Acute infection is therefore among the most important risk factors for stroke in young persons.\textsuperscript{116} For more than a century, the association between stroke and infection was recognized only in children and adolescents in whom established vascular risk factors are uncommon.\textsuperscript{117} However, several studies now suggest that recent infections are independent trigger factors for CVD also in adults, with in-
creased risk during or shortly after hospital admission for acute infection, and other studies suggest that vaccination against influenza and pneumonia may protect against CVD. Both bacterial and viral infections, particularly respiratory tract infections contribute to this association. The severity and type of host immune response, rather than the specific microbial agent, seems to influence CVD risk after infection. What is less well-established is whether a raised CVD risk remains in the years following severe infections and if there is a period of particularly heightened risk.

Multiple pathophysiological pathways could link infection and inflammation, thrombosis and CVD. Atherosclerosis is a chronic inflammatory disease that is believed to originate in childhood. It is an inflammatory response culminating in a plaque comprised of a core rich in lipids, pro-inflammatory cells and cytokines, and a fibrous cap. Inflammation is regarded as playing a central role in the atherosclerotic process from initiation of atherosclerosis to progression and rupture of plaques. Various pathways also link inflammation and coagulation. Infections may result in inflammatory responses, which may contribute to local and systemic inflammation, coagulation disturbances, induce ischemia, endothelial dysfunction and inflammatory changes in atherosclerotic plaques. The presence of acute inflammation in acute infections is frequently followed by a procoagulant state, which is characterised by activation of procoagulant pathways and inhibition of anticoagulant pathways, and these pathways probably represent one of the most important mechanisms underlying infection-associated CVD. Alone, or in combination, these effects can increase the short-term risk of cardiovascular events.

As heightened systemic inflammatory and procoagulant activity can persist long after infections resolve, the effect of infections on CVD risk could also extend for several years. However, the long-term effect of severe infections on the development of CVD remains uncertain, and the mechanisms by which infections could affect long term risk of CVD are poorly understood. Few studies have so far reported associations with severe infections and subsequent long-term risk of CVD. Characterising the risk of CVD after infection is important because it could identify a period when greater surveillance or use of interventions may be of particular benefit.
Sepsis (including bacteraemia) and pneumonia resulting in hospital admission are relatively common severe infections that have the potential to induce persistent inflammatory or other immunological changes. Sepsis is defined as the systemic inflammatory response syndrome that occurs during infection. It is generally viewed as a disease aggravated by the inappropriate immune response encountered in the affected individual. Morbidity and mortality are high. Pneumonia produces frequently high levels of circulating proinflammatory cytokines and is associated with significant morbidity and mortality.
SUMMARY

Cardiovascular disease (CVD), including stroke and coronary heart disease (CHD), is a leading cause of death and disability globally. Consequences of these diseases are associated with a huge burden of economic cost and individual suffering. Although typical clinical onset does not occur until adulthood, CVD may have a long natural history with accumulation of risks beginning in early life and continuing through childhood and into adolescence adulthood. Therefore, it is important to adopt a life-course approach to explore accumulation of risks, as well as identifying age-defined windows of susceptibility, from early life to disease onset. Adolescence is a particularly important period; childhood and adolescent development set the scene for future mental and physical health through physiological and behavioural mechanisms. Within a life-course framework, this thesis will examine risks for cardiovascular disease from adolescence, as well as from later adulthood, where exposures can pre-date disease onset significantly. One area of focus is on characteristics in adolescence, which reflect inherited and acquired elements from childhood, and their association with occurrence and characteristics of subsequent stroke and CHD many years later. Another focus is on infections in adulthood and risk of subsequent CVD.

Exposure to psychosocial stress has been linked with a variety of adverse health outcomes, including stroke and CHD, but the evidence to date is inconclusive. Stress resilience – a marker of susceptibility to stressful exposures – recorded prospectively in adolescence may be a useful measure for investigating the consequences of chronic stress in relation to stroke and CHD risk and outcome. The association of stress resilience with CVD may in part be explained by other risk factors already present in adolescence. Severe infections in adulthood have been associated with contemporaneous CVD risk, but less is known about the delayed CVD risk following such infections that may operate through inflammatory or other immunological pathways. The life-course approach adopted here will provide evidence of aetiological processes and pathways relevant to the development and characteristics of CVD.
AIMS

One set of aims of this thesis was to assess the extent to which physical, psychological and medical characteristics from adolescence are determinants of future risk for and outcomes following stroke and CHD. A life-course approach was adopted where these characteristics were used as indicators of previous exposures. Another aim was to investigate the role of serious infections in adulthood and the risk of CVD in subsequent years. All of the projects involved assessing independence from potential confounding factors and identifying aspects of the potential underlying mechanisms.

The following specific research questions were addressed:

- Is stress resilience in adolescence associated with subsequent stroke by middle age? Is this association explained by other known stroke risk factors from childhood and adolescence?

- Is stress resilience in adolescence associated with subsequent CHD by middle age, and what is the role of physical fitness in this association? 1) Is physical fitness a mediator to explain a component of the association between stress resilience and CHD risk? 2) Does the association of physical fitness with CHD risk vary by level of stress resilience?

- Is there an association between stress resilience and other known stroke risk factors from adolescence with hospital stay duration (indicating stroke severity characteristics) in middle-aged men?

- Are severe infections in adulthood associated with subsequent long-term risk of CVD?
MATERIAL AND METHODS

Study population – a conscription cohort

Data from several national Swedish registers were used to provide information on a general population-based cohort of men. Some 284,198 males, born in Sweden from 1952 to 1956 and included in the Swedish Military Conscription Register, form the primary basis of the study cohort for this thesis. This cohort represents the vast majority of males born in Sweden during this period, and thus this is a representative sample of the general population of men.

At this time, conscription and the associated examinations before entering military service were compulsory for all male citizens of ages 18 and 19 years, with a small number at later ages. Only men with significant disability, severe chronic disease or congenital disorder (such as mental disability, asthma, poorly controlled type 1 diabetes mellitus, deafness, psychiatric disorders, cerebral palsy, epilepsy, cardiac disorders, or severe drug abuse), or those in prison, were exempted from conscription, approximately 2-3% annually. The Conscription Register provides information of anthropometrics, medical diagnoses, physical, cognitive function, and psychological measures. The assessments were performed at any of six regional centres in Sweden, and included two days of extensive medical, psychiatric and physical examinations by physicians and psychologists. These data represent the main source for adolescent markers of future disease risk in this thesis.

Measures

Stress resilience

Our measure of stress resilience was derived from the psychological evaluation at conscription that consisted of cognitive and non-cognitive assessments, following a procedure that was adopted in 1969 and unchanged until 1995 when it was subject to minor revisions. An evaluation of stress resilience was obtained from a standardized interview with a certified psychologist. Prior to the assessments, all men filled in self-administered questionnaires on aspects of their familial, medical, social, behavioural and personality characteristics. The psychologists produced
ratings on their overall psychological and cognitive function by combining evaluations using questionnaires and the interview.\textsuperscript{142, 143}

All eligible men underwent the psychological examination including the assessment of their potential ability to cope with stress,\textsuperscript{140, 144} based on their ability to control and channel nervousness, tolerance of stress and disposition to anxiety.\textsuperscript{145} The potential conscripts met a trained psychologist for a semi-structured interview, usually lasting between 20 and 30 minutes. The interview psychologist followed a manual with certain topics to be discussed; however, specific questions were not decided beforehand. In this procedure, the psychologist asked about any adjustment problems and conflicts, as well as about successes, responsibilities taken on, and initiatives shown or experienced, in school, at work, in sports or other leisure activities, and at home.\textsuperscript{141, 144} The psychologists were instructed to first make a decision on the potential conscripts’ mental fitness. The aim was to assess if the men fulfilled the psychological requirements for military service, and ultimately of armed combat, thereby providing an indication of their stress resilience in adolescence.

Stress resilience is a compound variable of four psychological dimensions relevant to general everyday life; including social maturity, level and direction of interests, psychological energy, and emotional stability.\textsuperscript{143} Willingness to assume responsibility, independence, having an outgoing character, persistence, emotional stability, and ability to take initiative were regarded as the requirements for ‘high resilience’.\textsuperscript{141}

Social maturity included sense of responsibility, independence, extroversion and dominance, and was measured on a five-point scale. Psychological energy included estimations of ability to take initiative, perseverance, capacity to motivate activities in oneself and others, and the ability to fulfil incomplete plans and tasks (leadership abilities). Emotional stability involved the ability to control and channel nervousness, tolerance of stress and disposition of anxiety.\textsuperscript{145} The psychologists were instructed to ask the potential conscripts how they emotionally responded to important events and situations experienced in childhood and adolescence; occurring at school or the workplace, or in home environments. Emotional control was rated on a five-point scale. Ratings 1 (very poor) and 2 (poor) were given to men who had psychosomatic symptoms or anxiety, lacked the ability to regulate emotions effectively, or had difficulty controlling nervousness and aggression. Rating 3 (average) was given to conscripts who had adequate
emotional control, that is the absence of particularly negative or positive deviations. Ratings 4 (good) and 5 (very good) were given to individuals who appeared to respond calmly and purposefully, with good control of nervousness and aggression.\textsuperscript{146} Emotion regulation may relate to other constructs such as coping ability.

The overall psychosocial functioning variable (stress resilience) was constructed as a summary score between 1 and 9, following a normal distribution, with a mean of 5 and a standard deviation of 2. A high ranking on psychosocial functioning could be argued to bear similarities with low neuroticism, high conscientiousness, and high extraversion,\textsuperscript{144} and would thus be similar to a measure of personality found, for example, among traits of the currently-popular five factor model of personality traits.\textsuperscript{147} A low score could reflect something like type A behaviour.\textsuperscript{148}

To ensure consistent evaluation, a central authority supervised the instruction and training of participating phycologists, supported by a written manual,\textsuperscript{140} and the inter-rater reliability of the psychologists was regularly checked. The inter-rater reliability for the assessment of psychosocial functioning was found to be high ($r = 0.86$) in a test where 30 recorded interviews from 1972/1973 were scored by 30 psychologists.\textsuperscript{149} Some details of the test are only available in Swedish,\textsuperscript{150} and not all military information is available to the public. However, it has been used in other studies.\textsuperscript{140, 151, 152}

Higher values of this measure indicate greater stress resilience, and it has been associated with better physical and psychological health and higher social/political participation,\textsuperscript{145} military competence,\textsuperscript{153} lower suicide risk\textsuperscript{142} and better childhood health.\textsuperscript{140, 151} In our study, this normally distributed nine level scale was collapsed into three categories as low, moderate, and high resilience, with some 22\% in the least and 24\% in the most stress resilient categories. High resilience was used as the reference category.

**Cognitive function**

The assessment of cognitive function used the Swedish Enlistment Battery questions and included four dimensions: verbal ability, spatial recognition, logical-inductive ability (general knowledge) and technical comprehension. It was a written assessment with 40 questions in each domain.\textsuperscript{154-156} Verbal ability was measured as an ability to interpret and follow written instructions and identify synonyms. Spatial recognition tested the ability to visu-
alize manipulation of objects mentally and recognize objects in different positions. The logical-inductive test consisted of general knowledge, arithmetic, and other questions involving shapes and letters. The fourth test involved knowledge of basic mechanics and physics such as weights, levers, projectiles and trajectories, electricity and momentum. The results of each subtest were summed into a nine-grade normally distributed scale (ranging from 1 to 9), and the scales were then combined and transferred onto a new stanine scale as a measure of general intelligence.\(^{145}\)

**Physical fitness and anthropometrics**

Physical tests were performed by trained military personnel, after central instructions, to assess the potential conscripts’ physical suitability for military service. Physical working capacity was recorded using a well-validated electrically braked stationary cycle ergonometric test and it can be used to calculate a measure of cardiorespiratory fitness.\(^{157, 158}\) Maximal aerobic workload is highly correlated with maximal oxygen uptake (VO\(_2\) max),\(^{159}\) and its measurement using this bicycle ergometer test is highly reproducible.\(^{160}\) After a normal resting ECG, the test started with a five minute long sub maximal test directly followed by a maximal test with gradually increasing load until volitional exhaustion. Starting loads varied, depending on physical stature, history physical activity and medical history. In men with a medical condition or not allowing a maximal test, a submaximal test was performed or an estimate was derived for those with current infectious disease or other condition influencing physical stature, history of physical activity and medical history. The resulting value (watts) was transformed into scores with a range from 0 to 9.\(^{161}\)

Measurements of weight and height from conscription examinations were used to create a measure of BMI (kg/m\(^2\)). This variable was categorized using the WHO criteria of underweight (BMI <18.5), normal weight (BMI 18.5 to <25), overweight (BMI 25 to <30) and obesity (≥30).\(^{162}\)

**Health status**

Systolic and diastolic blood pressure was measured after rest in recumbent men using a sphygmomanometer. Erythrocyte sedimentation rate (ESR), is a marker of inflammation,\(^{163}\) which rises and falls slowly, and is therefore suitable for tracking inflammation among patient with chronic conditions.\(^{164, 165}\) ESR corresponds to the distance that a column of anticoagulated blood falls over a 1 hour period and was measured using the Wester-
ESR was categorized into the following groups: low inflammation (ESR <10mm/h), moderate inflammation (ESR >10 to <15 mm/h) and high inflammation (ESR 15+ mm/h) with the threshold for “moderate” and “high” ESR groups corresponding to the clinical cut-point for normal ESR among men in this age group. Analyses involving ESR were adjusted for erythrocyte volume fraction (EVF), as standard in analyses of ESR.

From the medical examination at conscription assessment, any diagnosis in adolescence was recorded using the International Classification of Diseases, eighth revision (ICD-8). The medical assessment produced a score of 0 to 9 to indicate the severity of any chronic illness or disability, where 9 indicated no diagnosis and 0 indicated a very significant health problem. We further identified diagnoses of any cardiovascular disease at the time of the conscription assessment by using the ICD-8 codes 393-458.

In papers II-III adjustment in sensitivity analyses was made for diabetes mellitus. Codes used for diabetes were 250 in ICD-8 and ICD-9, and E10-14 in ICD-10. In paper II sensitivity analyses with adjustment for men with psychiatric diagnoses was made. Codes for psychiatric diagnoses at conscription used were 290-299 (psychoses, n=435), 300-309 (neuroses, personality disorders and other nonpsychotic mental disorders, n= 34 503), and 310-315 (mental disability, n=4 809). In paper IV adjustment in sensitivity analyses was for the burden of disease. A Charlson Comorbidity Index score was calculated from data on diagnoses in the National Patient Register recorded by 1987, for dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes, hemiplegia, renal disease, cancer leukaemia, lymphoma and AIDS/HIV. Diagnoses of CVD were not included in the score as all men with these diagnoses before follow-up were excluded.

Infections
Severe infection (sepsis and pneumonia resulting in hospital admission) was used as the exposure variable in paper IV. Adult diagnoses were obtained though the Swedish National Patient Register from 1969 to 2010. This register was launched in 1964 and contains records of all inpatient diagnoses with complete coverage from 1987, including both main diagnosis and secondary diagnoses. More than 99% of all somatic and psychiatric hospital charges are registered. We used ICD codes to identify all
discharge dates for inpatient diagnoses of sepsis and pneumonia (including bacteraemia). Infections were considered as new-onset if more than 30 days after discharge from the previous episode. The codes used for pneumonia were 480-486 in ICD-8 and 9, and J12-J18 in ICD-10; for sepsis and bacteraemia 038 and 036.1 in ICD-8, 038, 036C and 790.7 in ICD-9 as well as A39.2, A40-41, A02.1, R65.1, R57.2 and A49.9 in ICD-10.169.

**Socioeconomic characteristics**

Use of the national registration numbers allows linkage across a number of general national population-based registers. The Total Population register combines several sources held by Statistics Sweden, and provides information including dates of birth, death and emigration. Other registers held by Statistics Sweden, including the Longitudinal database of Education, Income, and Occupation (LISA) and Population and Housing censuses provided socioeconomic information from 1960. These variables include parental occupations, residential region and household characteristics. Parental occupations of the cohort members and household crowding provide an indication of socioeconomic characteristics during childhood, and are being used as indicators of material circumstances. The head of household’s occupation was classified as manual, agricultural, farm owners/managers, office workers, business owners/managers, and others, to create a socioeconomic index (SEI). Household crowding was divided into two categories to indicate a ratio of less than two persons per room, or more or equal to two persons per room.

**Outcomes**

CVD diagnoses were studied as outcomes in all four papers (I-IV) in the thesis. Papers I and III specifically studied stroke, papers II and IV used CHD as the outcome, while all-cause CVD was included as an outcome in paper IV. The main information on disease outcomes was obtained from the National Patient Register and the Cause of Death Register. The Swedish Cause of Death Register was established in 1952 and the completeness exceeds 99%. This register includes information on specific causes of death obtained from death certificates, collected by local parish registries. The validity of CVD diagnoses in both these registers is quite high.171
Stroke
We identified the dates of first non-fatal and fatal stroke diagnoses during the period 1969-2010. The ICD codes used for stroke were 430-434 and 436 in ICD-8, 430, 431, 433, 434 and 436 in ICD-9; and I60, I61, I63, I64 in ICD 10. For ischemic stroke, they were 432-434 in ICD-8, 433, 434 in ICD-9, and I63 in ICD-10; for intracerebral haemorrhagic stroke 431 in ICD-8, 431 and 432 in ICD-9, and I61 in ICD-10; for subarachnoid haemorrhagic stroke 430 in ICD-8, 430 in ICD-9, and I60 in ICD-10.

For the definition of hospital stay duration (paper III) we identified nonfatal strokes and defined them as patients who survived at least 28 days. Fatal strokes were excluded in this definition as they would confound assessment of hospital stay duration. Duration in days (without discharge) as a hospital inpatient after the initial stroke was identified on the basis of the median duration of hospital stay; we defined long stay as one week or more and short stay as less than a week. Second stroke was defined as occurring at least 28 days after the first.

Coronary heart disease
The codes used for CHD were 410-414 in ICD-8 and ICD-9, and I20-25 in ICD-10. The codes used for acute MI were 410 in ICD-8 and ICD-9, and I21 in ICD 10. For angina pectoris, they were 413 in ICD-8, 413 and 411B in ICD-9, and I20 in ICD-10.

All-cause cardiovascular disease
The codes used for all CVD diagnoses were 390-458 in ICD-8, 390-359 in ICD-9 and I00-99 in ICD-10.

Exclusions for papers I-IV
The cohort consisted originally of 284 198 men of whom 2564 were excluded due to errors in the personal identification number, female sex, or uncertain vital status. Some 16 458 men did not complete the conscription examination due to chronic illness, disability, or lack of Swedish citizenship, these men are also excluded. Those with implausible values for height (less than 144 cm), weight (above 178 kg), body mass index, BMI, (below 15), systolic blood pressure (below 50 or above 230 mm Hg), and diastolic blood pressure (below 30 or above 135 mm Hg) were also excluded from analysis; in total 225 men. Exclusions for disease events prior
to follow-up from January 1, 1987 (papers I-III), for death, emigration and stroke or CHD diagnosis resulted in a sample of 271,767 men. We further excluded 37,196 men with missing data for stress resilience, disease summary score, year of birth, geographic region, systolic and diastolic blood pressure, BMI, cognitive function, physical working capacity, parental SEI and household crowding (including 722 men with a stroke diagnosis, and 2523 with a CHD diagnosis). A total of 237,879 men were available for analysis in papers I-III.

In paper IV, start of follow-up was from conscription assessment and exclusions for death, emigration or a diagnosis of all-cause CVD (n=6923), sepsis or pneumonia (n=158) was prior to conscription date, and further exclusions was for missing ESR data, resulting in a study sample of 236,739 men.

**Statistical analysis**

Men in the study cohort were followed from 1987 (when the National Inpatient Register received full coverage), or from the conscription assessment (paper IV), to date of first stroke, CHD or all-cause CVD diagnosis in adulthood, death emigration or 1st of January 2010, whichever occurred first. All analyses were conducted as cohort studies and utilized Cox regression with attained age as the underlying scale of analysis, wherever possible, in order to provide an accurate hazard estimate for the outcome measures and the most effective adjustment for age. Cox regression models were used for all four papers (I-IV) to investigate associations of the exposures with subsequent disease risk and outcomes. Analyses were performed using SPSS statistical software version 21 and 22, and Stata 13 (Stata Corp LP, Texas, USA). In paper II, mediation analysis was performed using R V.3.1.2. The proportional hazards assumptions for the association of exposures with outcomes was tested graphically, as well as using a test based on Schoenfeld residuals. Hazard ratios (HRs) were estimated with 95% confidence intervals (CIs) and statistical significance was defined as p<0.05.

In paper I survival analysis using Cox proportional hazards models was used to examine the association of stress resilience in adolescence with subsequent stroke risk. The Cox regression model accounts for person-years at risk and assumes that HRs during follow-up are proportional between exposure categories, in this case between the categories of stress
resilience.\textsuperscript{172} The HR is the main effect measure reported in many epidemiological studies, and defined as the hazard in the exposed group divided by the hazard in the unexposed group.\textsuperscript{173} Associations in paper I were examined using an unadjusted set of estimates and three further adjusted models. In model 2 adjustment was made for demographic and socio-economic factors from the cohort members’ family of origin (birth year, region of residence, parental SEI and household crowding). Model 3 was additionally adjusted for characteristics in adolescence (cognitive function, diastolic and systolic blood pressure and cardiovascular diagnosis at conscription). In model 4 physical fitness as markers of lifestyle factors (physical working capacity and BMI) were added to the model.

The same Cox regression models as in paper I were used in paper II, but with CHD as the outcome. In paper II we additionally performed mediation analysis\textsuperscript{174} to assess the mediating role of physical fitness in the association with stress resilience in adolescence and subsequent CHD. The objective of a mediation model is to identify pathways that underlie an observed relationship between an independent variable and dependent variable via the inclusion of a third mediating variable.\textsuperscript{175}\textsuperscript{174} The core element of mediation analysis is the estimation of direct and indirect effects, and the total effect is their estimate.\textsuperscript{176}

In paper II, we examined effect modification by stress resilience in the entire study population by multiplicative interaction testing. To investigate possible interactions between categorically modelled stress resilience and continuously modelled physical working capacity, we used the multivariate fractional polynomials interaction algorithm.\textsuperscript{177} We selected the linear interaction model as the most appropriate. We then tested the significance of the interaction terms using the commonly applied likelihood ratio test (LRT). The model was adjusted for the covariates included in Model 2 (paper II, table 2) including an interaction term (stress resilience as a categorical variable by physical working capacity modelled continuously), with adjustment for the main effects, thus identifying multiplicative interactions.\textsuperscript{178} Another model was further adjusted for BMI.

Joint Cox proportional hazard models\textsuperscript{179} were used in paper III to assess the associations of characteristics in adolescence with long versus short duration of hospital admission after first stroke (two different outcome possibilities). Joint Cox allowed the entire cohort to be examined together, even those without stroke. As stroke risk varies by age, we used age as the
underlying timescale with a method allowing us to include the entire cohort, not only those who experienced a stroke. This model estimated the ratio of the HRs for long and short stay, which can be interpreted similarly to conventional HRs. The model was adjusted for potential confounders in childhood and adolescence (geographical region, parental SEI, household crowding, and disease score at conscription); while measures of stress resilience, physical working capacity, BMI, cognitive function and blood pressure in adolescence were all included in the adjusted model, and therefore mutually adjusted for each other. Sensitivity analyses excluding strokes in earlier adulthood were performed as there might be greater aetiological heterogeneity between strokes at younger and older ages; strokes at younger ages were defined at ages 31 to 45 years and older strokes 46 to 58 years. Another sensitivity analysis was conducted for duration between first and second stroke; second strokes occurring after the first year of the initial event (and up to 20 years later) were excluded. Further sensitivity analyses were performed for men with intracerebral haemorrhage, who in addition had a diagnosis of subarachnoid haemorrhage (SAH). These men with SAH were excluded as the aetiology might be different and influence the risk of intracerebral haemorrhage. A last sensitivity analysis was adjusted for a diagnosis of diabetes mellitus.

In paper IV Cox regression was used to investigate the associations of serious infection in adulthood with subsequent CVD risk, with separate analyses for all-cause CVD and for CHD. Infection diagnoses were modelled as time-dependent covariates, and the outcome was identified at prespecified time intervals post-infection (0-1, >1-2, >2-3, >3-4, >4-5 and 5+ years after hospital admission for the infection). For the main analysis, follow-up started from the conscription assessment (earliest in 1969). Cohort members were excluded if they had received a diagnosis of CVD, sepsis or pneumonia by the time of conscription assessment. Adjustment was made for region of residence, SEI, and household crowding in 1960; and summary disease score, ESR and EVF, BMI, stress resilience, blood pressure, physical working capacity and cognitive function in adolescence. Sensitivity analysis examined if the delayed association between first infection and CVD is explained by subsequent infections where all infection diagnoses (of sepsis and pneumonia) are included in the adjusted model as time-dependent covariates. Another sensitivity analysis with follow-up
from 1987 investigated the possible cofounding effect of chronic disease in adulthood using the Charlson Comorbidity Index score.

**Ethical considerations**

The projects (including papers I-IV) were approved by the Regional Ethics Committee in Uppsala, Sweden (Dnr 2009/306 and 2014/324). The earlier approval was needed to create the cohort. As this is a retrospective register-based cohort study, with no intervention, written informed consent was not required from the study participants. Register linkage was performed by the governmental organizations responsible for the specific registers and all data have been de-identified to researchers, who undertook not to reveal the identity of any individuals. We therefore consider the risk of individual integrity breach as minimal, and outweighed by the potential benefits of the study results.
RESULTS

In summary, the main findings were:

- **Paper I**: Low stress resilience in adolescence is associated with an increased risk of stroke in middle aged men. This association is in part explained by other cardiovascular risk factors in adolescence and especially by physical fitness. The results are consistent for subtypes of stroke with higher magnitude associations for fatal stroke.

- **Paper II**: Low stress resilience in adolescence is associated with risk of CHD in middle age, and this association is in part mediated by low physical fitness among men with low stress resilience in adolescence. In addition, the protective effect of having high physical fitness is reduced or eliminated among men with low stress resilience.

- **Paper III**: Low stress resilience, underweight and higher systolic blood pressure in adolescence are associated with longer hospital stay (compared with shorter) after an ischaemic stroke. Elevated systolic and diastolic blood pressure in adolescence is associated with longer hospital stay in haemorrhagic stroke.

- **Paper IV**: Raised risks of CVD following hospital admission for sepsis or pneumonia were increased for more than five years after the infection, but with the highest magnitude during the first three years following infection.
Paper I

Characteristics of the study population by stress resilience categories are shown in table 1. Men with low stress resilience tended to have lower physical working capacity, lower cognitive functions scores, higher blood pressure, were underweight, overweight or obese, more often had a diagnosis of cardiovascular disease at conscription, and had parents with lower SEI and experienced greater household crowding in childhood.

Table 1. Population characteristics by stress resilience levels

<table>
<thead>
<tr>
<th></th>
<th>High (7-9) stress resilience N= 56 293 (%)</th>
<th>Moderate (4-6) stress resilience N= 129 746 (%)</th>
<th>Low (1-3) stress resilience N= 51 840 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parental SEI 1960</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual workers</td>
<td>19 107 (33.9)</td>
<td>55 116 (42.5)</td>
<td>24 622 (47.5)</td>
</tr>
<tr>
<td>Agricultural workers</td>
<td>1450 (2.6)</td>
<td>5318 (4.1)</td>
<td>2459 (4.7)</td>
</tr>
<tr>
<td>Farm owners/managers</td>
<td>5285 (9.4)</td>
<td>14 132 (10.9)</td>
<td>4324 (8.3)</td>
</tr>
<tr>
<td>Office workers</td>
<td>20 424 (36.3)</td>
<td>34 134 (26.3)</td>
<td>11 428 (22.0)</td>
</tr>
<tr>
<td>Business owners/managers</td>
<td>6954 (12.4)</td>
<td>13 817 (10.6)</td>
<td>4729 (9.1)</td>
</tr>
<tr>
<td>Others/unknown</td>
<td>3073 (5.5)</td>
<td>7229 (5.6)</td>
<td>4278 (8.3)</td>
</tr>
<tr>
<td><strong>Household crowding 1960</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 people/room</td>
<td>47 484 (84.4)</td>
<td>101 462 (78.2)</td>
<td>36 846 (71.2)</td>
</tr>
<tr>
<td>&gt; 2 people/room</td>
<td>8809 (15.6)</td>
<td>28 284 (21.8)</td>
<td>14 994 (28.8)</td>
</tr>
<tr>
<td>Cognitive function²</td>
<td>6.1 (1.7)</td>
<td>5.2 (1.9)</td>
<td>4.2 (2.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure² (mmHg)</td>
<td>71.3 (8.5)</td>
<td>71.6 (8.6)</td>
<td>72.1 (8.8)</td>
</tr>
<tr>
<td>Systolic blood pressure² (mmHg)</td>
<td>127.6 (11.1)</td>
<td>127.7 (11.1)</td>
<td>127.6 (11.2)</td>
</tr>
<tr>
<td><strong>CVD diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1479 (2.6)</td>
<td>3631 (2.8)</td>
<td>1521 (2.9)</td>
</tr>
<tr>
<td>No</td>
<td>54 814 (97.4)</td>
<td>126 115 (97.2)</td>
<td>50 319 (97.1)</td>
</tr>
<tr>
<td><strong>Physical working capacity²</strong></td>
<td>7.2 (1.7)</td>
<td>6.2 (1.7)</td>
<td>5.5 (1.7)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²) N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>3719 (6.6)</td>
<td>15 403 (11.9)</td>
<td>8535 (16.5)</td>
</tr>
<tr>
<td>Normal weight (18.5 to &lt;25)</td>
<td>48 623 (86.4)</td>
<td>104 698 (80.7)</td>
<td>38 892 (75.0)</td>
</tr>
<tr>
<td>Overweight (25 to &lt;30)</td>
<td>3624 (6.4)</td>
<td>8331 (6.4)</td>
<td>3660 (7.1)</td>
</tr>
<tr>
<td>Obese (≥30.0)</td>
<td>327 (0.6)</td>
<td>1314 (1.0)</td>
<td>753 (1.5)</td>
</tr>
</tbody>
</table>

* Mean (SD).

CVD, cardiovascular disease; SEI, socioeconomic index.

During follow-up from 1987 to 2010, we identified 3411 diagnoses of first stroke in our study population (1.4%). All characteristics investigated are statistically significantly associated with stroke. Lowest compared to highest stress resilience is associated with increased risk of all stroke with
a HR (and 95% CI) of 1.54 (1.40-1.70) as shown in table 2 (model 1). The association attenuated slightly after adjustment for socioeconomic characteristics in childhood (model 2) and development and disease in adolescence (model 3). The greatest reduction followed further adjustment for markers of physical fitness in adolescence (model 4), with an adjusted HR of 1.16 (1.04-1.29).

Table 2. All stroke risk associated with stress resilience and other characteristics in adolescence

<table>
<thead>
<tr>
<th>Stress resilience</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>Adjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1 HR (95% CI)</td>
<td>Model 2 adjusted for socioeconomic characteristics in childhood</td>
<td>Model 3 further adjusted for development and disease in adolescence</td>
<td>Model 4 further adjusted for physical fitness</td>
</tr>
<tr>
<td>High (7-9)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Moderate (4-6)</td>
<td>1.09 (1.00–1.19)</td>
<td>1.07 (0.98–1.16)</td>
<td>1.01 (0.92–1.10)</td>
<td>0.94 (0.86–1.03)</td>
</tr>
<tr>
<td>Low (1-3)</td>
<td>1.54 (1.40–1.70)</td>
<td>1.48 (1.34–1.63)</td>
<td>1.30 (1.18–1.45)</td>
<td>1.16 (1.04–1.29)</td>
</tr>
</tbody>
</table>

The results were consistent when stroke was divided into subtypes; fatal, haemorrhagic and ischaemic stroke. All outcomes showed statistically significant associations with stress resilience, with higher magnitude associations for fatal than non-fatal stroke; and for haemorrhagic than ischaemic stroke. In the adjusted models a similar pattern as for all stroke appeared, but the association of low stress resilience with ischaemic stroke was more notably attenuated by physical fitness. The fully adjusted HRs (95% CIs) for fatal stroke are 1.50 (1.04-2.16); for haemorrhagic stroke 1.28 (1.00-1.63); and for ischaemic stroke 1.08 (0.94-1.24).

**Paper II**

Some 10 581 diagnoses of first CHD were identified in the study population (4.4%). As for stroke (table 1), all covariates were statistically significantly associated with stress resilience, and also with CHD (all CHD, fatal CHD, acute myocardial infarction (MI), fatal MI and angina pectoris). Low stress resilience was associated with an increased risk of all CHD in
middle age (table 3), with an unadjusted HR of 1.65 (1.56-1.75), consistent with our results for stroke. The association attenuated slightly after adjustment for socioeconomic characteristics in childhood (model 2) and development and disease in adolescence (model 3). The greatest reduction followed further adjustment for markers of physical fitness in adolescence (model 4) with an adjusted HR of 1.17 (1.10-1.25).

**Table 3.** Risk of CHD associated with stress resilience, physical working capacity and BMI in adolescence

<table>
<thead>
<tr>
<th>Main exposure:</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>Adjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress resilience</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>High (7-9)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Moderate (4-6)</td>
<td>1.24 (1.18-1.30)</td>
<td>1.18 (1.12-1.25)</td>
<td>1.09 (1.02-1.15)</td>
<td>0.94 (0.98-1.09)</td>
</tr>
<tr>
<td>Low (1-3)</td>
<td>1.65 (1.56-1.75)</td>
<td>1.54 (1.45-1.63)</td>
<td>1.28 (1.21-1.36)</td>
<td>1.17 (1.10-1.25)</td>
</tr>
</tbody>
</table>

Mediator:

Physical working capacity (per unit change 0-9)

Body Mass Index (kg/m²)

Underweight (<18.5) 0.88 (0.83-0.94) 0.78 (0.73-0.83)

Normal weight (18.5 to <25) Reference Reference

Overweight (25 to <30) 1.76 (1.66-1.88) 1.63 (1.53-1.74)

Obese (≥30) 2.79 (2.47-3.15) 2.23 (1.97-2.52)

Model 2 adjusted for socioeconomic characteristics in childhood.
Model 3 further adjusted for development and disease in adolescence.
Model 4 further adjusted for physical fitness.

All outcomes for CHD subgroups showed a significant and graded association with stress resilience in unadjusted and adjusted models, with higher associations for fatal disease. The fully adjusted HRs (95% CIs) for the association of low stress resilience are: for acute MI 1.18 (1.08-1.28), for fatal MI 1.49 (1.16-1.90), for angina pectoris 1.18 (1.08-1.28) and for
fatal CHD 1.52 (1.27-1.83). Sensitivity analyses with adjustment for psychiatric disease by conscription showed similar results as the main analyses. Mediation analysis indicated that approximately 19% of the association between low stress resilience and CHD was mediated by physical working capacity. The inverse association of physical working capacity scores (modelled continuously as 0-9) with CHD was less pronounced in the low-resilience group when examined in stratified analysis (table 4). These results were consistent also when adjusted for BMI. We found that in men with low stress resilience the protective effect of having higher physical working capacity was reduced or eliminated. Statistically significant effect modification was confirmed by interaction testing.

### Table 4. Physical working capacity (per unit change; 0-9) and CHD stratified by stress resilience

<table>
<thead>
<tr>
<th>Sample size</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample size</td>
</tr>
<tr>
<td></td>
<td>Highest resilience group</td>
</tr>
<tr>
<td></td>
<td>Physical working capacity</td>
</tr>
<tr>
<td></td>
<td>Moderate resilience group</td>
</tr>
<tr>
<td></td>
<td>Physical working capacity</td>
</tr>
<tr>
<td></td>
<td>Lowest resilience group</td>
</tr>
<tr>
<td></td>
<td>Physical working capacity</td>
</tr>
</tbody>
</table>

*Adjusted for birth year, region of residence, parental SEI and household crowding.
**Further adjusted for BMI in adolescence.
*a Interaction term p<0.05 (Wald test).

### Paper III

Using the same cohort as in previous studies, a total of 3000 men between ages 31-58 years were diagnosed with first non-fatal stroke, and 791 of these also had a recurrent stroke during follow-up. Some population characteristics by first non-fatal and second stroke are shown in table 5. Compared with the stroke-free population, men with first non-fatal or second stroke more often had lower stress resilience, higher blood pressure, more overweight or obesity, lower cognitive function scores, lower physical fitness, very significant health problems, parents with manual or other/unknown occupations, and greater household crowding in childhood.
Table 5. Characteristics of the stroke-free population and men with first non-fatal and second stroke (not mutually exclusive)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Stroke-free cohort N=234 879</th>
<th>First non-fatal stroke N=3000</th>
<th>Second stroke N=791</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress resilience N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (7-9)</td>
<td>55 687 (23.7)</td>
<td>606 (20.2)</td>
<td>153 (19.3)</td>
</tr>
<tr>
<td>Moderate (4-6)</td>
<td>128 186 (54.6)</td>
<td>1560 (52.0)</td>
<td>401 (50.7)</td>
</tr>
<tr>
<td>Low (1-3)</td>
<td>51 006 (21.7)</td>
<td>834 (27.8)</td>
<td>237 (30.0)</td>
</tr>
<tr>
<td>Body Mass Index N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>27 334 (11.6)</td>
<td>323 (10.8)</td>
<td>97 (12.3)</td>
</tr>
<tr>
<td>Normal weight (18.5 to &lt;25)</td>
<td>189 881 (80.8)</td>
<td>2332 (77.7)</td>
<td>586 (74.1)</td>
</tr>
<tr>
<td>Overweight (25 to &lt;30)</td>
<td>15 333 (6.5)</td>
<td>284 (9.4)</td>
<td>82 (10.4)</td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>2331 (1.0)</td>
<td>63 (2.1)</td>
<td>26 (3.3)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)*</td>
<td>127.6 (11.1)</td>
<td>128.6 (11.4)</td>
<td>130.0 (11.4)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)*</td>
<td>71.6 (8.6)</td>
<td>72.9 (8.9)</td>
<td>73.3 (8.9)</td>
</tr>
</tbody>
</table>

* Mean (SD).

Low stress resilience, underweight, and higher systolic blood pressure (per 1-mm Hg increase) during adolescence are statistically significantly associated with longer hospital stay (compared with shorter) in ischaemic stroke as shown in table 6. Elevated systolic and diastolic blood pressure is associated with longer hospital stay in men with intracerebral haemorrhagic stroke. Among both stroke types, obesity in adolescence conferred an increased risk of second stroke (compared with first stroke without recurrence), with an adjusted HR of 2.06 (1.21-3.45). In sensitivity analyses that excluded strokes at younger ages, and longer duration than one year from first to second stroke, the results were consistent with the main analyses (data not shown). Further sensitivity analyses excluding patients with haemorrhagic strokes who in addition had a diagnosis of subarachnoid haemorrhage also showed similar results to the main analyses. The last sensitivity analysis adjusted for a diagnosis of diabetes mellitus showed only a small reduction in magnitude of associations.
Table 6. Joint Cox model to estimate associations of characteristics in adolescence with long compared to short hospital stay in ischaemic (n=1978) and haemorrhagic (n=503) stroke

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ischaemic stroke</th>
<th>Haemorrhagic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR long stay/</td>
<td>HR long stay/</td>
</tr>
<tr>
<td></td>
<td>HR short stay</td>
<td>HR short stay</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Stress resilience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (7-9)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Moderate (4-6)</td>
<td>1.23 (0.97–1.56)</td>
<td>1.24 (0.73–2.11)</td>
</tr>
<tr>
<td>Low (1-3)</td>
<td>1.46 (1.08–1.98)</td>
<td>1.67 (0.88–3.17)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>1.41 (1.04–1.91)</td>
<td>0.68 (0.38–1.26)</td>
</tr>
<tr>
<td>Normal weight (18.5 to &lt;25)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Overweight (25 to &lt;30)</td>
<td>0.82 (0.59–1.12)</td>
<td>1.13 (0.62–2.08)</td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>0.70 (0.38–1.24)</td>
<td>3.98 (0.50–31.43)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.01 (1.00–1.02)</td>
<td>1.01 (1.00–1.03)</td>
</tr>
<tr>
<td>(per 1-mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.00 (0.99–1.01)</td>
<td>1.02 (1.00–1.04)</td>
</tr>
<tr>
<td>(per 1-mmHg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for region of residence, parental SEI, household crowding in 1960; physical working capacity, cognitive function, cardiovascular disease and summary disease score at conscription.

**Paper IV**

This study included 236 739 men. During the follow-up period from conscription assessment to 2010, 46 754 men (19.7%) received a first diagnosis of CVD from age 18 to 58 years, including 10 279 with CHD (4.3%). A total of 9987 hospital admissions for sepsis and pneumonia were identified in 8534 men. As shown in table 7, men in this cohort were ostensibly healthy at conscription assessment, with most reporting either no diagnosis (45.3%) or no serious medical problem (38.6%). Men with CVD and CHD in adulthood were more likely to have lower levels of physical working capacity, lower cognitive function scores, poorer stress resilience, higher levels of ESR and obesity, as well as higher proportion with health problems in adolescence.
Table 7. Characteristics of the study population and men with cardiovascular disease (CVD) and coronary heart disease (CHD)

<table>
<thead>
<tr>
<th>Life course characteristics</th>
<th>Total cohort N=236 739</th>
<th>CVD N=46 754</th>
<th>CHD N=10 279</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adulthood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for first severe infection N(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8529 (83.6)</td>
<td>3694 (7.49)</td>
<td>869 (8.5)</td>
</tr>
<tr>
<td>No</td>
<td>228 210 (96.4)</td>
<td>43 060 (92.1)</td>
<td>9401 (91.5)</td>
</tr>
<tr>
<td>Hospitalization for recurrent infections N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only first infection</td>
<td>7416 (87.0)</td>
<td>3046 (82.4)</td>
<td>705 (81.1)</td>
</tr>
<tr>
<td>Recurrent episodes</td>
<td>1113 (13.0)</td>
<td>648 (17.6)</td>
<td>164 (18.9)</td>
</tr>
<tr>
<td>Adolescence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease at conscription N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diagnosis</td>
<td>107 271 (45.3)</td>
<td>19 284 (41.3)</td>
<td>4015 (39.1)</td>
</tr>
<tr>
<td>No serious health problem</td>
<td>91 391 (38.6)</td>
<td>18 602 (39.8)</td>
<td>4153 (40.4)</td>
</tr>
<tr>
<td>Fairly significant health problem</td>
<td>24 997 (10.6)</td>
<td>5655 (12.1)</td>
<td>1329 (12.9)</td>
</tr>
<tr>
<td>Significant health problem</td>
<td>18 080 (5.5)</td>
<td>3213 (6.9)</td>
<td>7373 (7.5)</td>
</tr>
<tr>
<td>ESR (mm/h) N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;10)</td>
<td>227 885 (96.3)</td>
<td>44 896 (96.0)</td>
<td>9821 (95.6)</td>
</tr>
<tr>
<td>Moderate (10 to &lt;15)</td>
<td>4750 (2.0)</td>
<td>949 (2.0)</td>
<td>206 (2.0)</td>
</tr>
<tr>
<td>High (15+)</td>
<td>4101 (1.7)</td>
<td>909 (1.8)</td>
<td>243 (2.4)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m2) N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>27 410 (11.6)</td>
<td>4703 (10.1)</td>
<td>1003 (9.8)</td>
</tr>
<tr>
<td>Normal weight (18.5 to &lt;25)</td>
<td>191 532 (80.9)</td>
<td>36 683 (78.5)</td>
<td>7907 (77.0)</td>
</tr>
<tr>
<td>Overweight (25 to &lt;30)</td>
<td>15 486 (6.5)</td>
<td>4433 (9.5)</td>
<td>1110 (10.8)</td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>2311 (1.0)</td>
<td>935 (2.0)</td>
<td>250 (2.4)</td>
</tr>
<tr>
<td>Stress resilience N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (7-9)</td>
<td>56 550 (23.9)</td>
<td>10 130 821.7</td>
<td>1931 (18.8)</td>
</tr>
<tr>
<td>Moderate (4-6)</td>
<td>128 771 (54.4)</td>
<td>25 109 (53.7)</td>
<td>5516 (53.7)</td>
</tr>
<tr>
<td>Low (1-3)</td>
<td>51 418 (21.7)</td>
<td>11 515 824.6</td>
<td>2822 (27.5)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>127.5 (11.0)</td>
<td>128.7 (11.2)</td>
<td>129.1 (11.0)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71.6 (8.6)</td>
<td>72.5 (8.8)</td>
<td>72.8 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Physical working capacity*</td>
<td>6.3 (1.8)</td>
<td>6.2 (1.8)</td>
<td>6.1 81.8</td>
</tr>
<tr>
<td>Cognitive function*</td>
<td>5.2 (2.0)</td>
<td>5.0 (2.0)</td>
<td>4.7 (2.0)</td>
</tr>
<tr>
<td>Childhood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental SEI 1960 N(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual workers</td>
<td>98 014 (41.4)</td>
<td>20 474 (43.8)</td>
<td>4741 (46.2)</td>
</tr>
<tr>
<td>Agricultural workers</td>
<td>9139 (3.9)</td>
<td>2000 (4.3)</td>
<td>537 (5.2)</td>
</tr>
<tr>
<td>Farm owners/managers</td>
<td>23 496 (9.9)</td>
<td>4365 (9.3)</td>
<td>887 (8.6)</td>
</tr>
<tr>
<td>Office workers</td>
<td>65 986 (27.8)</td>
<td>12 019 (25.7)</td>
<td>2370 (23.1)</td>
</tr>
<tr>
<td>Business owners/managers</td>
<td>25 604 (10.8)</td>
<td>4799 (10.3)</td>
<td>981 (9.6)</td>
</tr>
<tr>
<td>Others/unknown</td>
<td>14 501 (6.1)</td>
<td>3097 (6.6)</td>
<td>754 (7.3)</td>
</tr>
<tr>
<td>Household crowding 1960 N(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 people/room</td>
<td>50 689 (21.8)</td>
<td>11 062 (23.7)</td>
<td>2724 (26.5)</td>
</tr>
</tbody>
</table>

*Mean (SD).
In the unadjusted and adjusted model, the highest magnitude association with an increased risk of CVD is during the first year after first infection. A notably raised risk persists over two years after the infection, and then the magnitude attenuates with time but remains statistically significant after five years (table 8). Raised risks for CVD are associated with the following factors in adolescence: higher inflammation (ESR), higher blood pressure, overweight and obesity, low stress resilience, poorer cognitive function, poorer physical working capacity and diagnoses influencing daily life. In childhood, manual occupations and greater childhood crowding are associated with an increased CVD risk. Similar results were observed for the CHD outcome subgroup.

<table>
<thead>
<tr>
<th>CVD</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of Events</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>First infection</td>
<td>45 277</td>
<td>Reference</td>
</tr>
<tr>
<td>Up to 1 year after infection</td>
<td>301</td>
<td>6.62 (5.91–7.42)</td>
</tr>
<tr>
<td>&gt;1-2 years after infection</td>
<td>105</td>
<td>2.59 (2.13–3.13)</td>
</tr>
<tr>
<td>&gt;2-3 years after infection</td>
<td>85</td>
<td>2.22 (1.79–2.74)</td>
</tr>
<tr>
<td>&gt;3-4 years after infection</td>
<td>71</td>
<td>1.95 (1.54–2.46)</td>
</tr>
<tr>
<td>&gt;4-5 years after infection</td>
<td>67</td>
<td>1.96 (1.54–2.49)</td>
</tr>
<tr>
<td>5+years after infection</td>
<td>848</td>
<td>1.60 (1.50–1.71)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHD</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of Events</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>First infection</td>
<td>9836</td>
<td>Reference</td>
</tr>
<tr>
<td>Up to 1 year after infection</td>
<td>68</td>
<td>4.70 (3.71–5.97)</td>
</tr>
<tr>
<td>&gt;1-2 years after infection</td>
<td>42</td>
<td>3.28 (2.42–4.44)</td>
</tr>
<tr>
<td>&gt;2-3 years after infection</td>
<td>29</td>
<td>2.45 (1.70–3.53)</td>
</tr>
<tr>
<td>&gt;3-4 years after infection</td>
<td>26</td>
<td>2.36 (1.61–3.47)</td>
</tr>
<tr>
<td>&gt;4-5 years after infection</td>
<td>22</td>
<td>1.95 (1.41–3.25)</td>
</tr>
<tr>
<td>5+years after infection</td>
<td>256</td>
<td>1.73 (1.53–1.96)</td>
</tr>
</tbody>
</table>

Adjusted for birth year, region of residence, parental SEI, household crowding in childhood; ESR and EVF, stress resilience, physical working capacity, cognitive function and summary disease score at conscription.
ESR, erythrocyte sedimentation rate; EVF, erythrocyte volume fraction; SEI, socioeconomic index.
Sensitivity analyses allowing further adjustment for adult-onset diseases produced significant results between serious infections and CVD only of slightly lower magnitude than the main analysis. The Charlson Comorbidity Index score was used to capture adult disease, and this analysis began follow-up from 1987. Similar results were observed for the CHD outcome subgroup. In another sensitivity analysis adjustment was made for subsequent infections (modelled as time-dependent covariates), showing that these later episodes attenuates the estimates somewhat, but does not eliminate them, indicating that recurrent infections does not explain the associations. When the infections, sepsis and pneumonia, were analysed separately, the associations were similar to the main results for both infections combined, with slightly higher magnitude estimates for sepsis.
DISCUSSION

Stress resilience in adolescence and risk of stroke and CHD in middle age

Main findings
Results from papers I-II, both general population-based cohort studies of men, demonstrate that low stress resilience in adolescence is associated with higher risk of stroke and CHD in middle-aged men. These associations were somewhat attenuated by adjustment for childhood socioeconomic circumstances, as well as health and developmental characteristics in adolescence. The associations were further attenuated, but not eliminated by adjustment for physical working capacity and BMI as indicators of physical fitness in adolescence, likely to signal future lifestyle characteristics. Some of the association with CHD was mediated through lower physical working capacity among those with lower stress resilience. As expected, better physical fitness in adolescence was associated with lower risk of CHD, but it is noteworthy that this association was attenuated or eliminated in men with low stress resilience.

Social and biological pathways over the life-course
Adverse social and material conditions in childhood could influence risk of later stroke and CHD, and also shape both personality traits and the stress response. But adjustment for such factors had little impact on the association of stress resilience with stroke and CHD. The small reduction in magnitude confirms that those of lower stress resilience are at higher risk of stroke and CHD independent of their measured background characteristics. Psychological stress at any point in the life course has been linked with higher cardiometabolic risk; a recent study suggests that even if distress in childhood appears to have resolved by adulthood, it might still signal early CVD risk. Our results are consistent with the literature suggesting a role for psychosocial stress in influencing CVD risk, including a recent meta-analysis suggesting that perceived psychosocial stress is independently associated with increased risk of stroke. Methods to measure stress in previous studies have been heterogeneous, and clear causal inference has been difficult to establish. Reporting bias due to the use of retrospectively collected information has been a potential...
problem in some previous case-control studies.\textsuperscript{17, 18, 96-98} While some prospective studies have been performed, with conflicting results,\textsuperscript{182, 183, 188, 189} short duration of follow up in studies measuring stress in middle-aged subjects is unlikely to capture significant chronic accumulation of risk relevant to the long natural history of CVD. It is also possible that stressful exposures in middle age are confounded by other previously accumulated cardiovascular risks. A further issue is that there are between-individual differences in what constitutes stressful exposures and the ability to cope with them. Adjustment for potential pathways from childhood and adolescence that could explain an association with stress resilience and CVD could increase our understanding of disease mechanisms.

It has been demonstrated that early life stress (that could in theory increase the risk of low stress resilience) has been linked with impaired development; including cognitive function,\textsuperscript{190} blood pressure control mechanisms,\textsuperscript{102} and greater disease susceptibility in later life.\textsuperscript{75, 76, 89} As elevated glucocorticoid levels, resulting from stress arousal, can impair cognitive function,\textsuperscript{191} lower cognition can also be a consequence of chronic stress. Childhood stress has also been associated with subsequent unhealthy weight gain,\textsuperscript{192} where overweight may be a consequence of low exercise levels.\textsuperscript{193} Cognitive function, blood pressure and physical fitness in adolescence may therefore, in part, already represent consequences of earlier stressful exposures and poorer stress resilience, and adjusting for these characteristics is arguably an over-adjustment in our models. Some of the increased risk for stroke and CHD is likely to operate through lower physical fitness which is a well-established risk factor for stroke and CHD. We suggest that a proportion of the association of stress and stress resilience with stroke and CHD is explained by behavioural/lifestyle processes, as also suggested by previous studies.\textsuperscript{194} However, our results further suggest that these processes may begin in childhood or adolescence. Overweight, obesity and poorer physical capacity in adolescence are likely to signal an accumulation of health risks that continue through adulthood.\textsuperscript{86, 88} Other lifestyle risks in the years between conscription and stroke/CHD, such as smoking, alcohol consumption and diet, are also likely to be mediating factors. Another potential mediating influence may be type 2 diabetes, which tends to have its onset in adulthood several years after conscription. Diabetes type 2 is also linked with psychosocial stress and stress resilience.\textsuperscript{195, 196-198}
It is notable that interaction testing revealed that among those with lower stress resilience, the beneficial association with higher physical fitness was eliminated. Physical fitness may fail to offer as great a protective effect in the face of other exposures associated with low stress resilience. Alternatively, those with low stress resilience who had high levels of physical fitness in adolescence may have failed to maintain such a high fitness level into later adulthood. To maximize the benefits associated with physical activity, adherence plays a vital role. Physical activity levels have been shown to decrease significantly between ages 9 to 15 years. Public health strategies to promote increased physical activity for children and adolescents, in particular among potential vulnerable or disadvantaged individuals, such as perhaps those with low stress resilience could be of importance.

Although low stress resilience appears to influence behaviour relevant to physical fitness, our results indicate that the association with stress resilience and CVD may not be explained entirely through behaviour. There may also be more direct neuroendocrine influences of stress, particularly among those with low stress resilience and thus greater susceptibility to stress leading to chronic arousal. Chronic stress may involve autonomic nervous system reactivity and overexposure to stress-responsive adrenal hormones, such as cortisol and catecholamine with long-term consequences for blood pressure and cardiovascular health. Shortened telomere length and decreased telomerase levels have been proposed as links between chronic psychological stress and cardiovascular disease, but whether there is a causal association requires further research. Other, potential mechanisms may involve initiation and maintenance of chronic inflammation, as well as metabolic influences relevant to insulin signaling and blood lipids.

**Characteristics in adolescence and stroke severity**

*Our findings in relation to previous research*

Stroke-related hospital stay duration and recurrent stroke are relevant for patient suffering, societal costs and use of health care resources among stroke survivors. We demonstrated that low stress resilience in adolescence can affect health across the life-course as indicated by associations with raised risk stroke and CHD, but also of depression and anxiety in middle age. As markers of childhood stress have been associated with higher
blood pressure in later life, we hypothesise that low stress resilience may influence stroke risk and outcome in adulthood in part through elevated blood pressure. Recent animal studies suggest that elevated HPA axis activation by prenatal stress, and stress in adulthood could diminish motor recovery after ischemic lesion in a rat model,\textsuperscript{207,208} thus suggesting a potential influence on stroke severity. The emergence of adult blood pressure variation between individuals begins in early childhood and becomes greater with age.\textsuperscript{209-211} Therefore, early detection of a maladaptive stress response and elevated HPA axis activation, after first stroke, might suggest new targets for interventions to reduce both stroke risk, and also morbidity and use of health care resources.

We did not find an association with length of hospital stay or second stroke for all characteristics in adolescence. Possibly because factors associated with fatal stroke might be less notably associated with non-fatal stroke outcomes due to higher fatality among cohort members with those characteristics. Although obesity is a risk factor for stroke,\textsuperscript{212} and especially for fatal stroke in our cohort (with an adjusted HR (and 95% CI) of 2.14 (1.71–2.68) and 3.99 (2.31–6.74) for all stroke and fatal stroke respectively), the relationship between pre-stroke BMI and post-stroke outcomes is less clear. It is possible that a high stroke-related fatality rate among obese men would attenuate the association with severity among survivors through a selection effect. Obesity is related to mortality in the general population but in stroke patients underweight has been found to be associated with even higher increased mortality risk,\textsuperscript{213,214} consistent with our results. Our findings from a male population where underweight in adolescence is associated with stroke severity, might suggest that underweight in adolescence could be marker of early disease susceptibility. Even BMI in adolescence could, in part, be a consequence of lower stress resilience.\textsuperscript{192} Both underweight,\textsuperscript{215} and low stress resilience,\textsuperscript{206} in adolescence have been linked with anxiety and depression in later life, diseases that are possible intermediate factors for stroke risk that could also influence stroke severity.\textsuperscript{216} Despite the lack of association with duration of hospital stay, obesity was strongly associated with second stroke in our population. This could be a chance association, but we speculate that this might be explained by aetiological difference as there is a possibility that the second strokes were of a different subtype than the initial event; a first ischemic stroke might have been followed by a haemorrhagic stroke.
Infections in adulthood and cardiovascular disease

Main findings
A first episode of sepsis or pneumonia infection in adulthood was associated with a notably increased risk of CVD that persisted for several years after the infection. The magnitude of association was highest in the year following infection, but remained at a relatively high magnitude for up to three years and was not eliminated after five years. Results were similar when a less heterogeneous outcome, CHD, was examined. We defined our exposure as two relatively common serious infections that require inpatient treatment as previous studies have shown that inpatient-treated infections are associated with higher risk of CVD than less severe infections treated in primary care.\textsuperscript{125, 129}

Our findings in relation to previous research
The high short-term risk of CVD after serious infections is well established,\textsuperscript{122} while findings from some studies addressing long-term effects of infections for CVD have been conflicting.\textsuperscript{118, 217-220} The result of this study is consistent with a small number of previous studies that have found a delayed association with CVD risk after severe infection.\textsuperscript{135, 137, 138} Corrales-Medina et al investigated pneumonia,\textsuperscript{135} while the research by Ou et al\textsuperscript{137} and Jafarzadeh et al\textsuperscript{138} was concerned with sepsis and bacteraemia. We investigated both types of exposure, as they appear to represent similar risks for CVD. Jafarzadeh et al, found a 5-year increased risk of CV events following sepsis and bacteraemia. Corrales-Medina et al report an increased risk of CVD after hospital admission for pneumonia that persisted for several years, while Ou et al found an increased risk of all-cause mortality and CVD in sepsis survivors persisting for up to five years. Unlike the work presented here and by Corrales-Medina et al, neither of the two latter studies characterised risk year-by-year immediately after infection, potentially not describing a window of particularly raised risk. None of these three recent studies examined directly whether the persistent raised risk following infection was due to reinfection by sepsis, bacteraemia or pneumonia. We investigated this potential explanatory mechanism and our results indicate that recurring infections is not an important explanation for the associations. Although able to adjust for a relatively large number of potential confounding factors, none of the previous studies were able to adjust for characteristics in childhood or adolescence.
The mechanisms by which infections could influence long-term risk of CVD require further investigation. Delayed CVD risk associated with first infection may represent a process mediated by persistent immunological or metabolic changes following infection, rather than due to subsequent infections. Persistent systemic inflammatory activity which could follow infection is a known risk factor for CVD. Although most patients with sepsis or pneumonia recover, many continue to exhibit high circulation inflammatory markers after the acute phase of infection. Inflammation and coagulative pathways are linked, and inflammation in acute infections is frequently followed by a procoagulant state, which is characterized by activation of procoagulant pathways and inhibition of anticoagulant pathways, and probably represents one of the most important mechanisms underlying infection-associated CVD. Heightened pro-coagulant activity can persist long after infections resolve, resulting in an extended period of several years where heightened CVD risk exists.

**Interpretation from a life-course perspective**

Different periods in life may be associated with differences in pattern of risk accumulation, sometimes independent and sometimes clustered or accumulated. Our results from papers I-III indicate that childhood and adolescence may have an important role in the determination of long-term cardiovascular health, but later influences are also important, as shown in paper IV. Low stress resilience measured in late adolescence was more common among men from families with lower parental SEI and greater household crowding. Men with lower stress resilience further tended to have lower physical capacity scores, lower cognitive function scores, higher blood pressure, were more likely to be underweight, overweight or obese, or more often had a cardiovascular diagnosis at conscription in late adolescence. Childhood socioeconomic circumstances can influence early life risk factors for subsequent CVD. Such associations could in part reflect an impact of stress in early life, working through biological mechanisms or adverse behavioural responses to such disadvantage.

Early stress may influence stress resilience, and in turn lower stress resilience may influence development of physical fitness, BMI, cognitive function and blood pressure over the life-course. Early stress and stress resilience could possibly contribute to an accumulation of risks from early life and onwards. Risk of CVD in middle age may be accumulated from early
life and onwards as the number, duration, and severity of exposure increase, possibly resulting in cumulative damage to biological systems. One pathway is likely to operate through behavioural mechanisms, particularly by mediation of physical fitness, while other metabolic pathways also are likely to exist although not examined in this thesis. These different pathways of risk have implications for intervention and prevention strategies for CVD.

Later windows of vulnerability are also likely to influence CVD risk. In paper IV we demonstrated an association with severe infections in adulthood and subsequent delayed CVD risk, independent of risk factors from adolescence. Persistent systemic inflammatory activity which could follow infection, and that might persist long after infections resolve, represents one possible mechanism.

Methodological considerations

Study design
The level of accuracy of results in either observational or experimental studies is based on their precision and validity. Findings from virtually all studies are affected by a varying degree of limitations. Therefore, describing the appropriate design and addressing the potential limitations is useful for both planning and interpreting the findings of a study. A cohort is simply a group of people who share some characteristic, and in a cohort study participants are followed over time. Typically, the exposure is measured in the individual and the subjects are followed longitudinally until they develop the outcome of interest, die or the study period ends. If the exposure measures are collected prospectively and the study is longitudinal then the quality can be higher. All studies in this thesis (papers I-IV) have a cohort design with objectively and prospectively collected information and a long follow up from childhood to middle age.

Bias and confounding
A confounder constitutes a third factor which is associated with both exposure and outcome, without being an intermediate step in the causal pathway from the exposure to the outcome. Confounding factors influence or confuse the risk estimation with the effect of another factor. A limitation of our use of statistical adjustment to tackle potential confound-
ing is that we can only adjust for confounders that we have measured and identified. Therefore, residual (or unmeasured) confounding may be a potential threat to interpretation of this as well as many other observational studies. In our study, we chose to adjust for covariates that on a theoretical basis could act as confounders. These included characteristics in childhood and CVD risk factors from adolescence and early adulthood, all measured before start of follow-up. To examine pathways we also adjusted for potential intermediate characteristics in papers I-II, where we adjusted for developmental characteristics and physical fitness in adolescence; although we hypothesised that these could be an over-adjustment. As we have used stress resilience as a marker of some potential earlier exposures, we cannot be definitive about the exact biological mechanisms and exposures responsible for them.

Potential types of bias include selection bias and information bias. Selection bias occurs if those selected for a study – or those with the outcome or exposure of interest - are different from those not selected – or without exposure/outcome - in a systematic way. This type of bias tends to be more common in case-control studies, if controls do not represent the same source population as the cases. In a cohort study all subjects can represent the same source population, but selection bias might be caused by differential loss to follow-up. To reduce the impact of selection effects in paper III we analysed the entire cohort, and not only those who had experienced a stroke. In the subset with stroke, men with the most severe strokes, fatal strokes, would be lost, and as expected, analyses of characteristics in adolescence in men with a stroke diagnosis showed that previously identified risks for stroke were notably associated with fatal stroke creating selection bias among the survivors.

Death from causes other than CVD could be regarded as a competing risk in all four studies, as the subject cannot receive a CVD diagnosis after death from other causes. The influence of competing events could be more important in studies of older people and potentially could result in a dilution of associations.

The general population-based national cohort design limited selection bias, as this is a broadly representative sample of the male population. Only a few percent of the men were exempted from conscription examinations due to chronic disease or disability. Among the remaining men with missing data on covariates of interest (37 196 men), 77% had conditions
that made them ineligible for conscription and no further testing was undertaken. Thus, the cohort is somewhat selected for better health at baseline. All information linked to the conscription data were obtained from national registers with very low rates of missing information. Thus, it is unlikely that inclusion in the cohort was strongly associated with predictors investigated in the studies.

Misclassification arises when incorrect measurement of the exposure or outcome occurs in a study. If this is systematic, it can lead to bias in the estimation of the association between exposures and outcomes.

**Exposures**

In this thesis we used objectively and prospectively collected information from conscription assessments in late adolescence, therefore the risk of recall bias, often present in case control studies, is reduced. Although derived from extensive medical, psychiatric and physical examinations by trained physicians and psychologists, with high completeness, some misclassification of the variables of interest is not unlikely.

In previous studies, resilience factors have often been measured based on self-report or interview using scales which focused on some specified dimensions of resilience, but in our data it was evaluated by psychologists by summarizing various dimensions related to everyday life. There is a possibility of misclassification of the stress resilience measure if conscripts attempted to obtain exemption from military service due ‘false’ answers. Whether such misclassification would be differential with regard to outcome is difficult to predict, but ‘false’ answers, if they exist, would most likely dilute the resilience measure and result in less precise estimates.

The conscription ergometer testing during the 1970s in Sweden was not primarily used for aerobic fitness testing and has a fairly low correlation with the maximal oxygen uptake test if not adjusted for weight. Although we have not adjusted for weight, we use the information from the ergometer test as a marker of the cohort members’ physical working capacity, as a component of physical fitness. Some 12% of our study population had an *estimated* physical working capacity test; this was performed for conscripts when a full test could not be undertaken due to current infections or other causes. However, sensitivity analyses in paper II excluding these men did not markedly change the associations with the CHD outcomes;
therefore differential misclassification from this source is not likely to explain the results.

BMI was calculated using measurements of height and weight at the conscription examination. It was most likely an accurate measurement of individual differences in BMI in late adolescence. However, differences in BMI are used to indicate leanness, overweight and obesity. As a measure of under- or overweight in adolescent men in terms of body adiposity differences, BMI has limited precision. BMI is also a function of high muscle mass and in particular in young men. 228 BMI might therefore misclassify body adiposity and cause an underestimation of body adiposity and CVD outcomes. This is a particular problem for the overweight category, as where the BMI value signifies obesity, there is more likely to be central adiposity.

Blood pressure measurements were performed on the first day of the conscription examination, after 5-10 minutes of rest. Unless the measure was outside a ‘normal’ interval, only one measurement of blood pressure was taken. Measurement imprecision with regard to blood pressure might be somewhat larger with single measurements, than in studies with more standardized protocols. Both systolic and diastolic blood pressure seems to have been rounded to the nearest 5 or 10 mmHg. Non-differential misclassification of blood pressure measurements, due to single measurements and rounding, might have resulted in less precise estimates of associations with CVD outcomes.

Outcomes
Outcome data for diagnoses of stroke, CHD and CVD are based on information from the National Patient Register and the Cause of Death register, registers frequently used in epidemiological studies in Sweden. The validity of some diagnoses recorded in the National Patient Register can be questionable, but the validity of commoner diagnoses such as stroke, CHD and CVD are satisfactory, 171, 229, 230 however there is a risk of misclassification especially of intracerebral haemorrhagic strokes, angina pectoris and sepsis. A high specificity but a somewhat reduced sensitivity may still suffice to minimize the number of false-positive diagnoses. 171 The proportion of valid diagnoses in the National Patient Register is probably higher in patients with more severe disease. A minor proportion of all-cause CVD (I00-I02 and I05-I09) may not be directly relevant in relation to infections. Length of hospital stay is recorded accurately but might be
affected by other factors such as availability of beds and rehabilitation facilities, discharge possibilities, and local practice.\textsuperscript{231} Such non-differential misclassification would however only reduce the precision of our results rendering more conservative estimates.

**Limitations**

This project has some potential limitations. These include the inclusion of only men. This was necessary as the measures of determinants in adolescence were collected during military conscription, which at the time was almost exclusively available to men. Women are also affected by stroke and CHD. It has been demonstrated that women develop CHD as frequently as men, although some 10 years later in life.\textsuperscript{232, 233} Women are protected from accelerating atherosclerosis by sex-related hormones (especially oestrogen).\textsuperscript{234} When this protection begins to decrease after the menopause, the risk of clinical cardiac events increases.\textsuperscript{235} There is no strong evidence that the processes involved in resilience would differ among men and women, although there may be important sex differences in behaviour. Subtle differences in brain architecture might lead to different strategies for men and women concerning stress in daily life, but more research is needed to study if biology and the stress response mechanisms may differ among men and women.\textsuperscript{49} Sex-related hormones may influence stress susceptibility during critical periods during the life-course.\textsuperscript{236 237 238}

Stroke onset typically occurs at an older age than in our study; early stroke may be somewhat atypical and aetiologically different from stroke at older ages.\textsuperscript{239} However, CVD, including stroke, has particularly devastating consequences at these somewhat younger ages as in our cohort, with the potential for greater life-time burden of disability, and because some risks may be modifiable. Stressful exposures were not examined, and the interaction of stress resilience with stressful exposures was not evaluated. It is possible that the magnitude of association with CVD risk for stress resilience is influenced by this. We cannot be definitive about the temporal relationship of stress resilience and other measures in adolescence. Due to the cross-sectional nature of the conscription examination measures we are not able to disentangle whether low stress resilience may have influenced some of the other measures in adolescence. However, as low stress resilience is likely to have its origins in earlier life we hypothesise that poor stress resilience could have an adverse influence on physical
fitness, cognitive function and blood pressure. As stress resilience was measured only once, we cannot be definitive about stability of this characteristic over time, but associations with outcomes later in life suggest persistence. The other characteristics measured at conscription examinations can also change in the years following adolescence before CVD onset.

Unfortunately, we have no data on smoking or hypercholesterolemia, which could have added to our understanding of lifestyle risks. We believe that smoking might be a consequence of low stress resilience and therefore act as a mediator for a component of the association with CVD risk. However, we cannot exclude the possibility that if smoking is implicated in the association, then pre-existing smoking may in turn influence stress resilience and may be one of the factors that reduce the protective effect of better physical fitness among men with low stress resilience. Aerobic capacity (VO₂ max) has been reported to be 7% lower in 18-year-old male smokers compared with non-smokers, thus smoking is unlikely to account for more than a small proportion of our observed association with physical working capacity and CHD. As our estimates in paper IV are based on the first episode of infection we will most likely have produced conservative estimates of association, but examining multiple repeated infections may make causal inference more difficult as developing CVD may be driving infections risk increasingly. Even though the results are similar for both sepsis and pneumonia, we cannot be certain if other infections would have the same patterns of persistent association with CVD. Finally, as with almost all observational studies, there is a possibility of unmeasured potential residual confounding factors which might have influenced the estimates.

**Clinical relevance and public health implications**

The first three papers in this thesis are among some of the first to use stress resilience in adolescence as a measure of susceptibility to psychosocial stress, rather than measuring stressful exposures, in relation to cardiovascular disease and stroke risk. Stress resilience provided a useful tool to explore aetiological processes and pathways of risk accumulation that may help guide future early interventions aimed at reducing morbidity and mortality from cardiovascular disease including stroke. The mechanisms explaining the association found with stress resilience and stroke and CHD risk work partly through other CVD risk factors such as physical
fitness, unhealthy BMI and elevated blood pressure, all modifiable risk factors. The possibility of detecting risks from childhood and onwards, offers possibilities to target public health intervention both at the societal level by investing in childhood or in social environment, and at individual level by preventing diseases though behavioural or treatment interventions. Our results suggest that effective CVD prevention might focus on promoting both physical fitness and coping with stress.

The association with severe infections in adulthood and subsequent delayed CVD provides additional evidence for the importance of prevention of severe infections in adulthood; and the period immediately following such infections may represent a time for targeted interventions for CVD.

**Future studies**

Proposed research for the future will complement our earlier work by identifying causes of low stress resilience. This includes investigating how the stress response may be influenced by prenatal and early life stress. Exposures considered stressful during early life could influence development of the physiological control of the stress response. Animal studies show that early life stress impairs the negative feedback regulation of the stress response and thus increases the risk of the damaging consequences of a more chronic stress arousal, and thus low stress resilience. As we have shown that low stress resilience is linked with an increased risk of stroke and CHD, it is important to establish the extent to which exposures in infancy are responsible for setting stress resilience in the general population.

Significant pain and discomfort during infancy, including from therapeutic procedures or serious infections during the first year of life, is a form of stressful exposure linked with adverse outcomes in later childhood. But its influence on the nascent stress response and thus stress resilience is largely un-investigated in humans. The proposed study will use Swedish registers to create a large cohort of individuals that experienced diagnoses and procedures during the first year of life associated with significant pain and discomfort. The main outcome will be the measure of stress resilience in adolescence that we have used in this thesis. The study will evaluate developmental and chronic disease to ensure that early-life influences on the stress response are not due to related disease in later childhood. The research will confirm whether there is an age-specific win-
dow of susceptibility to painful experiences in infancy with life-long consequences for stress resilience, and whether the results from animal studies apply to human infants.

How the process involved in resilience differs between men and woman is another important challenge for future research, and while we will not have the measure of stress resilience from the conscription assessment for most women we will have the opportunity to examine other outcomes such as blood pressure that may signal control of the stress response.
CONCLUSIONS

Our findings indicate that some aspects of stroke and CHD risk have their origins in childhood and adolescence:

- Psychosocial stress and stress resilience in adolescence may be implicated in the aetiology of stroke and CHD, working in part through other cardiovascular risk factors, in particular physical fitness.

- Stress resilience, unhealthy BMI and elevated blood pressure in adolescence are associated with aspects of stroke severity (indicated by duration of hospital admission and risk of second stroke) among survivors of a first stroke.

Our findings indicate that exposures in adulthood may confer additional CVD risk:

- Risk of a first CVD diagnosis can remain persistently raised for several years following hospital admission for sepsis or pneumonia, but particularly during the first three years following infection, suggesting a time when patients may benefit from additional monitoring and interventions to protect against cardiovascular events.
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SVENSK SAMMANFATTNING

Hjärtkärlsjukdom är en ledande dödsorsak i västvärlden och stroke utgör den vanligaste orsaken till neurologiskt handikapp hos vuxna. Även om hjärtkärlsjukdom vanligtvis inte visar sig kliniskt förrän senare i livet, finns data som tyder på att sjukdomen kan ha ett långt naturlförlopp med start redan i barndomen, och att det är ackumulering av olika riskfaktorer under hela livstiden som avgör risken för hjärtkärlsjukdom. Syftet med avhandlingsprojektet var att undersöka hur fysiska och psykiska egenskaper i sena tonåren (som också utgör potentiella markörer för tidigare exponeringar i barndomen) är kopplade till risken för – och svårighetsgraden av – stroke och kranskärlsjukdom många år senare. För att vidare undersöka risker i ett livsloppsperspektiv studerade vi sambandet mellan infektioner i vuxen ålder och långtidsrisken för efterföljande hjärtkärlsjukdom.


och lunginflammation) medför en ökad risk för hjärtkärlsjukdom, inte bara i samband med infektionen utan även under flera år efteråt.

Sammanfattningsvis visar dessa studier att både fysiska och psykiska risk- och prognosfaktorer för stroke och kranskärlssjukdom kan identifieras redan under sena tonåren. Svåra infektioner senare i livet kan också medföra en långsiktig riskökning för hjärtkärlsjukdom. Förutom att bidra med etiologiska ledtrådar ger studieresultaten en fingervisning om möjligheter till intervention i ett livsloppsperspektiv.
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