

**Understanding sick leave risk in a lifecourse framework.
A register-based birth cohort study of Norwegians
born 1967–1976.**

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SUMMARY

Background

Sick leave rates in Norway and in the Western world in general are quite high, and despite the identification of a wide array of risk factors, much of the individual variation in sick leave remains unexplained. Health, education, occupation, individual abilities and traits, are all in part determined by conditions during the early lifecourse, and are also strong predictors of sick leave. However, few studies take a lifecourse approach to studying sick leave, instead often focusing only on more contemporary risk factors. One line of research has studied the importance of physical fitness on sick leave risk, though focusing primarily on adult fitness levels; poor fitness in adolescence could arguably have more far-reaching consequences, through its impact on educational and occupational attainment. A second line of research has focused on identifying pathways linking adult social position to sick leave, though these studies have rarely taken into account the individual and social conditions that precede adult conditions. Thus, it is difficult to say whether the observed findings are causal because early lifecourse factors could be confounding the association, and it also obscures the lifelong processes that lead to adult sick leave risk. Another line of work has focused on the role that social interaction may play in accounting for the patterns of clustering of sick leave risk, with some suggesting that this mechanism could account for observed sex differences in sick leave behavior. This research has mostly focused on the influence of neighborhoods and workplaces, but this norm-based mechanism could also be operating within families, with parents influencing offspring, and siblings influencing one another.

Aim

In this thesis, I sought to first identify pathways linking exposures to sick leave risk through occupational and educational trajectories while taking into account contributions of early lifecourse factors. In Paper I, we aimed to assess the impact of adolescent aerobic fitness on sick leave in adulthood, through the mediating variables education and work-related factors (industry and enterprise-mean sick leave level). We restricted the analysis to musculoskeletal diagnoses. In Paper II, the main exposure is adult social position, and the mediating variable is physical workload. Here we focused on taking into account early personality development and childhood and adolescent social conditions. Second, we sought to investigate possible familial social interaction, focusing in Paper III on intergenerational transmission of sick

leave, and sex-specific differences, and on sibling transmission from an older to a younger sibling in Paper IV. To account for the reverse causality problems and correlated effects in Paper IV, we used a *dynamic Cox survival model* that allowed for the incorporation of frailty and lagged time-dependent exposures.

Study population

We used four different study samples of employed individuals for the four papers based on certain selection criteria. All participants were identified from a national birth cohort study comprising all individuals born alive in Norway from 1967 through 1976. In Paper I, the sample was restricted to 227,201 males with available aerobic fitness information data from the National Conscription Database. In Paper II, the sample was restricted to 3,328 individuals from the birth cohort who had also participated in the Nord-Trøndelag Health Study (HUNT3, 2006–2008). In Paper III, we restricted the sample to 78,887 individuals, born 1974–1976, whose parents had been employed when the participants were 18. In Paper IV, our sample was 19,634 participants with one older sibling, where both siblings had been employed for at least four months.

Statistical methods

Data on exposures, outcomes and covariates were obtained from national registries, including the event-history database FD-Trygd (with data from 1992 through 2009) and from HUNT3. Our data thus spanned several decades, with some containing information on daily event-histories. The natural methodological choice for such a data structure is survival analysis, which was used for Papers I, II and VI. Due to the exposures of interest in the four papers having been being measured at different time-points, the respective follow-up periods also differed, ranging from 1 to 15 years. In Paper I, we used a traditional epidemiological approach to mediation analysis by fitting a *Cox regression model* with and without the mediators, while controlling for possible confounders (parental education, intelligence, BMI, and musculoskeletal fitness). In Paper II, we applied a *counterfactual approach to mediation*, based on an *Aalen's additive hazards model*. The model controlled for possible confounders (childhood and adolescent social position and neuroticism). In this analysis, we sought to identify the proportion of sick leave cases that could be reduced among individuals in the lowest adult social positions, if one could intervene to improve their physical workload so that it was the same as the physical workload of those with the highest adult social position. In Paper III, we estimated the additive risk difference in those exposed to parental sick leave at

age 18, compared to those not exposed, using *binomial regression*, in a model controlling for several early lifecourse confounders. To elucidate whether the association was likely attributable to social interaction, we considered the strength of the parental-offspring associations in different constellations of parent-offspring sex and diagnostic categories. In Paper IV, we fit a *dynamic Cox regression model* for recurrent events, to study whether sick leave hazard increased following exposure to an older sibling's sick leave episode. The model included both sibling sick leave and past sick leave history as *time-dependent covariates*. The latter was included in order to try to incorporate propensity to sick leave into the model. The model also controlled for a wide array of early life course and other time-dependent confounders.

Results

Aerobic fitness at age 18 was moderately associated with sick leave hazard 5 to 15 years later. Poor and medium fitness increased the rate of non-injury sick leave, but decreased the rate of injury sick leave. While the association between aerobic fitness and sick leave appeared to be mediated through education and work-related factors, the indirect pathway had a negative sign for non-injury sick leave, but a positive sign for injury-sick leave. In Paper II we found that if we could perform an intervention that would change the physical workload of the lowest social group to that of the highest, we could reduce 24% of the extra sick leave episodes due to the social gradient for women, and 30% for men. To our knowledge, this study is the first to show that the link between social position and sick leave through physical workload was confounded by neuroticism and childhood and adolescent social position, especially for women. In Paper III, we found evidence of a parent-offspring association of sick leave. Parental sick leave in adolescence was associated with offspring sick leave 15 years later, though we found no evidence of a stronger additive association for women than for men. The sick leave risk was generally stronger for exposure to sick leave in same-sex parent, and sick leave in same-diagnostic category. In Paper IV, we found that exposure to sibling sick leave was followed by an increased sick leave rate. The hazard also increased with increasing levels of exposure in a dose-response manner. Controlling for a dynamic covariate of past sick leave history only reduced the estimates slightly. However, we found that the pattern was substantially weakened when we re-analyzed the data from time-of-first sick leave episode to time-to-recurrent episodes, suggesting that most of the association could be due to an unobserved propensity to sick leave.

Conclusion

In conclusion, a greater understanding of the ways in which educational and occupational pathways interact with individual factors across the lifecourse is required. Adolescent aerobic fitness level was a risk factor for sick leave, and while this link appeared to be mediated through educational and work-related factors, and possibly also moderated, future studies should clarify this relation using causal mediation approaches that suited for survival outcomes and that can incorporate interactions between the exposure and mediator. This thesis further suggests that interventions aimed at reducing physical workload could reduce the social gradient in health. Additionally, we found that the link between adult social position and sick leave, and the mediating path through work conditions, may in part be due to personality factors and early life social conditions. This has implications for policy, but also for which variables future studies ought to consider in their analysis, since leaving them out will tend to show an inflated effect of adult social position on sick leave. In addition, a greater understanding of possible social influence within families is warranted. While we found that adolescent exposure to parent sick leave was associated with sick leave in adulthood, and sibling exposure was followed by an increased sick leave hazard, we could not rule out confounding. Studies that are able to adequately control for shared genetic vulnerability in family studies of sick leave, or studies that use a causal inference approach that evades this issue (i.e., natural experiments), are needed. Findings from the sibling study suggest that social interaction studies that do not take into account frailty may be biased. Further, it is still unaddressed which mechanisms are accounting for this possible social interaction—norms, information, or health behavior—which would also be important for intervention efforts.

LIST OF PAPERS

Paper I

Kristensen, P., Corbett, K., Mehlum, I.S., Bjerkedal, T. (2012). Impact of aerobic fitness on musculoskeletal sickness absence 5–15 years later: A cohort study of 227 201 male Norwegian employees. *Occupational and Environmental Medicine*, 69:250-255.

Paper II

Corbett, K., Gran, J.M., Kristensen, P., Mehlum, I.S. (2015). Adult social position and sick leave: the mediating effect of physical workload. *Scandinavian Journal of Work, Environment, and Health*, 41(6):542-553.

Paper III

Kristensen, P., Corbett, K., Mehlum, I.S. (2015). The gender gap in sickness absence from work and the influence of parental absence on offspring absence 15 years later: Register-based cohort of Norwegians born in 1974–1976. *BMC Public Health*, 15:684.

Paper IV

Corbett, K., Røysland, K., Kristensen, P., Mehlum, I.S. Assessing sick leave associations dynamically in a cohort of Norwegian siblings. Submitted 2015: *European Journal of Epidemiology*.

1 INTRODUCTION

Sick leave rates are in high in Norway, and medically certified sick leave has been found to be a strong predictor of future disability (Kivimäki et al., 2004) and all-cause mortality (Head et al., 2008). The financial cost to the Norwegian welfare society is staggering. Research that will improve our understanding of what causes sick leave could potentially lead to interventions that would have tremendous public health benefits. A large amount of empirical work has been conducted which has led to the identification of contemporary determinants of sick leave. This work has increased our understanding of how poor health, hazardous work environment, educational attainment, demographic factors, and social insurance systems influence the risk of sick leave. Despite the identification of all these risk factors, researchers still struggle to account for the variation in individual sick leave, suggesting that important explanations are being left out of the equation. One area that is seldom included in studies on sick leave is earlier conditions in life. This omission is somewhat puzzling, considering that conditions earlier in life have been found to be important for other health outcomes, and have in a few studies also found to be important risk factors for disability pension and sick leave. The focus of taking into account how social patterning throughout the lifecourse, not just contemporary factors, influences the development of disease, is a central principle in the theoretical discipline of lifecourse epidemiology (Ben-Shlomo & Kuh, 2002), yet this framework is rarely applied in the sick leave literature.

Why might it be important to take into account early life conditions and individual factors in considering the risk of sick leave in adulthood? First, lifecourse research has established that conditions in childhood and adolescence have an impact on adult health, and it seems plausible that there could be a similar effect for sick leave. That is, individual traits and exposures during childhood could have far-reaching impacts on adult sick leave. There may be hitherto unidentified risk factors early in life accounting for adult sick leave risk. Secondly, by identifying these early lifecourse risk factors, one might uncover pathways by which these early factors are operating. Childhood conditions and early individual traits are important for educational and occupational trajectories, which are also strongly related to sick leave risk. These pathways are rarely studied in conjunction with early lifecourse factors, but studying these pathways in light of the confounding issues relating to early childhood conditions and individual traits is important in order to get unbiased estimates. Another mechanism of risk transmission linked to early social conditions could be norms. Social interaction has been implicated as an explanation for apparent clustering of sick leave behavior, though arguably

the people who are the most important for our formation of norms and other sick-leave related behavior are our parents and sibling during early lifecourse development.

The purpose of this thesis is to study the effects of conditions during social upbringing on paid sick leave among adults, through the lens of a lifecourse framework where risk is seen as developing already in childhood and adolescence. I will start by first giving an overview of sick leave, and past research in the sick leave literature. I will then describe the lifecourse framework, which implies that the social conditions under which we grow up have far-reaching consequences for outcomes later in life, and ways in which past sick leave literature have used this framework in studying sick leave. Finally, I will present the main topics in this thesis.

1.1 Scope of the problem

Sick leave rates are high in Scandinavian countries compared to other parts of the world (OECD, 2010). It is somewhat difficult to compare sick leave prevalence across nations, due to the differing nature of the workforce, gender composition, and different rules for sick pay (Brage et al., 2002). Nonetheless, sick leave proportions in Norway are among the highest in OECD countries, along with other Scandinavian countries and the Netherlands. Figure 1, obtained from a report prepared by Proba Research (2014), displays the sick leave prevalence over the past decade in the Nordic countries, the Netherlands and Great Britain. The sick leave proportion in Norway was lowest in 1996 at 4.3%, and highest in 2009 when the proportion of sick leave days had reached 7%. Until 2006, only Sweden and the Netherlands had a higher sick leave proportion than Norway, but since then Norway has had the highest levels. This figure reflects the overall trends in OECD countries where an increasing trend in medical benefits has been reported (OECD, 2010; Ose, 2010). Generally, women tend to have higher sick leave rates than men (Ose, 2010). While some of this difference can be accounted for by changes in the workforce and pregnancy-related sick leave, the sex gap in sick leave is still unaccounted for (Kostøl & Telle, 2011).

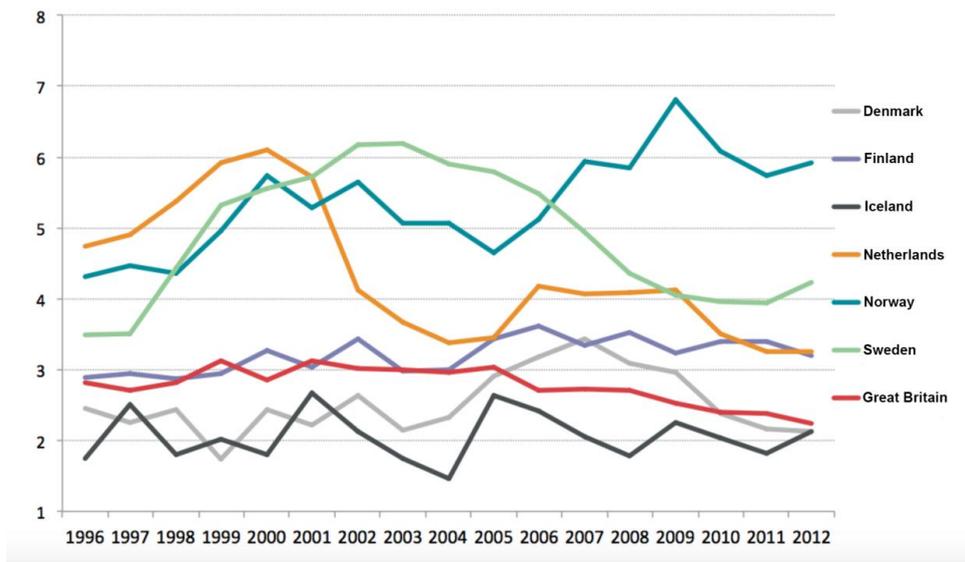


Figure 1. Development in mean sick leave percent from 1996 through 2012.

Source: Adapted from Proba Research (2014)

The costs of sick leave are very high. In 2015, the cost of sick pay for the Norwegian state was estimated to be 39.6 billion NOK, which amounts to 9.5 % of the estimated social insurance costs (Minsitry of Finance, 2015). If one includes the cost of disability pension—which can in some ways be seen as the trajectory of those individual who do not ever return to work from sick leave—that amount increases to more than one third of the state’s social insurance budget. The cost of sick leave is not limited to public sector, as employers are obliged to cover sick pay for the first 16 consecutive days of a given sick leave spell, with the annual cost in the private sector estimated to be in the billions (Hem, 2003). But the fiscal costs are obviously not the only problematic aspect about the high sick leave rates in Norway. Sick leave is considered a measure of overall health (Kivimäki et al., 2003) and is a predictor of mortality (Vahtera, Pentti, & Kivimäki, 2004) among the working population, and as such the high sick leave rate constitutes a major public health problem. In addition, Markussen (Markussen, 2012) shows that sick leave also has negative future financial implications for the individual, in that it leads to lower income in the future, and a higher risk of falling out of the workforce.

1.1.1 Brief overview of sick leave research approaches and explanatory models

There is no overarching theoretical framework that has guided the research approaches in sick leave research. Rather, a wide array of scientific disciplines have used different theoretical models and methodological approaches. The lack of a unifying framework is most likely due to the complex etiological process leading to sick leave, where the cause of sick leave is due to a multitude of individual and societal factors, specific to time and space. A summary of the theoretical approaches used in nearly 100 studies identified through a literature review was presented by Allebeck and Mastekaasa (2004a), with more recent updates presented by Ose, Jensberg, Reinertsen, Sandsund and Dyrstad (2006) and Ose (2010). While Allebeck and Mastekaasa's publication is now more than ten years old, and much sick leave research has been published in the intervening time, it nonetheless remains a highly relevant piece of work that I will present here in broad strokes.

As laid out by Allebeck and Mastekaasa (2004a), the bulk of sick leave research has been conducted within the scientific disciplines of medical science, sociology, psychology, and economics, often using research approaches with study designs and study populations specific to their field. In *medical science*, they identified two main research fields: clinical studies and epidemiological studies. In the clinical studies, the study sample is usually patients, whereas in epidemiological studies, the study sample is usually employees in a population sample. In clinical studies, the methodological approach is usually randomized clinical trials where the aim is to study the effects of treatment on the individual level. In epidemiological approaches, however, the research approach often focuses on designs where exposures that are not manipulated¹ by the researcher are studied in relation to an outcome, and where the study sample is usually population based. In *sociology*, the focus is often on conditions in society and the living conditions of individuals. Research in this field has tended to focus either on group characteristics (e.g., sex and education) or on conditions to which individuals are

¹What Allebeck and Mastekaasa (Allebeck & Mastekaasa, 2004a) write is that epidemiological research designs focus on “exposures that cannot be manipulated.” Later in the same paragraph, they write what seems to contradict this very sentiment: “there is usually a focus on opportunities to reduce risk factors in populations, or on interventions (i.e., workplace interventions) to reduce the scope of sick leave.” I therefore take their first statement to mean that they think epidemiological approaches focus on studies where the *researchers* do not manipulate the exposure of interest, rather than the exposure itself being non-manipulatable by nature, or by future interventions (e.g., age or sex).

exposed (e.g., work environment). In *psychology*, the study objectives are similar to medicine in that the focus is on reducing harmful effect on an individual level. Personality and different psychological and psychosocial characteristics are often the focus of interest, and study designs tend to be based on self-report questionnaires. Lastly, in *economics*, the study focus tends to be on economic incentives to be absent or present at work, seen in relation to an individual's rational choice-making behavior.

As for the explanatory models used to study sick leave, there have been certain theories that have been dominant in the various scientific fields. In organizational psychology, the theory surrounding "*withdrawal behavior*" due to low job satisfaction has been central. Various forms of withdrawal factors, or "pull factors," are considered as a reason for sick leave. A central area of focus is the influence of low work satisfaction, though often other factors such as personal characteristics and the social environment are taken into consideration. Another explanatory model that has been central not only to psychological literature, but also to fields such as medicine and sociology, is *stress theories*. This approach often focuses on specific diagnoses and types of psychological symptoms, such as anxiety and depression, as causes of sick leave. One stress theory, applied specifically to the work situation, is Karasek's "demand-control" or job-strain" theory, which has received the greatest attention. His theory highlights two situations of the work environment (demand and control) as being important for physical and psychological health and employee motivation. Sick leave research also includes stress factors outside of work, and the stress concept has been linked to sociological role theories. For instance, the higher sick leave of women has been studied from the theoretical standpoint of stress resulting from conflicting demands or expectations at home versus at work. Theories on *attitudes* and *cultures* had at the time the paper by Allebeck and Mastekaasa (2004a) was published, not received much attention, except in a few occupational and psychological approaches. However, in the past decade there has been an increased focus on social interaction in part determining sick leave risk, in particular within economics, where the social interaction is generally implied to be due to a change in norms or attitudes regarding sick leave behavior. Another central theory in economics is that the sick leave *insurance system* is assumed to influence sick leave behavior, and a generous system will lead to higher sick leave rates. In addition, the *labor market conditions* have been central in understanding the temporal changes in sick leave rates.

Allebeck and Mastekaasa (2004a) conclude the chapter by stating that more theoretically driven and interdisciplinary research is needed, specifically within the field of medicine, where they argue studies are often lacking explicit theoretical foundation. Another deduction

that it is possible to make from their overview, is that most of the explanatory models and research approaches focus on *contemporary* causes of sick leave. The individual's choices in response to the social insurance or labor market is studied as a direct response to the current surroundings, rather than as the result of individual vulnerability, even though it is known that certain individuals are most at risk. Working conditions are generally studied in relation to current exposures at work, sometimes in relation to family and social situations. But what is to a very large extent absent from the model is earlier lifecourse factors. It is not random who ends up with the unhealthy jobs, or who ends up being affected by labor shortage. Conditions early in life are important for a person's health, educational trajectory, attitudes, and many other factors that could be related to sick leave in adulthood. In the theoretical frameworks that are usually applied, sick leave appears to be viewed as an "event," though more recent work has focused on the importance of viewing sick leave as more of a process that develops over time (Henderson, Clark, Stansfeld, & Hotopf, 2012). Viewed in this light, one needs to cast a broader net if one wishes to get closer to a causal understanding of sick leave.

1.1.2 Sick leave approaches and risk factors

Many risk factors for sick leave have been identified. The aim of this section is to briefly present an overview of known risk factors, based in large part on a literature review by Allebeck and Mastekaasa (2004b). In addition, I have included select pieces of evidence from more recent studies.

Regarding *demographic factors*, the evidence relating to gender is very clear, with women having consistently higher sick leave risk than men (Laaksonen, Mastekaasa, et al., 2010; Mastekaasa & Dale-Olsen, 2000). Increased age and incidence of divorce is associated with higher sick leave risk, though the evidence on marital status in general and number of children is less clear (Allebeck & Mastekaasa, 2004b). A host of *lifestyle factors* have also been identified as risk factors for sick leave, including: smoking (Allebeck & Mastekaasa, 2004b), being overweight (Jans, van den Heuvel, Hildebrandt, & Bongers, 2007), physical exercise (Lahti, Laaksonen, Lahelma, & Rahkonen, 2010b) and physical fitness (Eriksen & Bruusgaard, 2002). *Mental health* factors are also predictors of sick leave, including common mental disorders like anxiety and depression (Henderson, Glozier, & Holland Elliott, 2005; Koopmans et al., 2010; Stansfeld et al., 1995), insomnia (Sivertsen, Øverland, Bjorvatn, Mæland, & Mykletun, 2009), and personality disorders (Gjerde et al., 2013). Studies on *labor market conditions* tend to find that sick leave is higher when unemployment is low. Results from studies regarding the *insurance system* are more mixed, though there is moderate

evidence that a higher potential income loss is associated with a reduced risk of sick leave. A more recent focus has been on *social interaction*, in which there appears to be a direct influence according to sick leave behavior of colleagues (Hesselius, Johansson, & Nilsson, 2009; Hesselius, Johansson, & Vikström, 2013; Rieck & Vaage, 2012) and neighbors (Hesselius, Johansson, & Vikström, 2008).

The literature on *socioeconomic status* is very consistent, with many studies finding that there is a clear social gradient in sick leave risk according to social position (Christensen, Labriola, Lund, & Kivimäki, 2008; Kristensen, Bjerkedal, & Irgens, 2007; Kristensen, Gravseth, & Bjerkedal, 2010; Melchior et al., 2005; North et al., 1993). Studies conducted on the work environment are closely linked to social position. A report in 2010 summarized the results on the importance of *work environment* within the health sector, finding that psychosocial risk factors (high demand, low control), organizational factors (night shifts, temporary employment), and mechanical factors (perceived physical workload) were all risk factors for increased sick leave (Sterud, Knardahl, Labriola, & Lund, 2010). Allebeck and Mastekaasa (Allebeck & Mastekaasa, 2004b) consider there being evidence of an increased risk due to physical working environment, and a moderately increased risk due to low control. Another important individual factor that has emerged as a risk factor for sick leave, is low intelligence (Henderson et al., 2012; Kristensen et al., 2010), tied closely to low attainment of socioeconomic position.

In line with the theoretical research approaches guiding the study of sick leave, the identified risk factors are primarily contemporary factors (Allebeck & Mastekaasa, 2004b). However, it is well established that conditions earlier in life influence later outcomes, but this has received very little attention in the sick leave research. Allebeck and Mastekaasa (2004b) review the evidence of the risk factors being causally related to the outcomes, and conclude that it is difficult to make any causal inference due to selection mechanisms and early social conditions rarely being controlled for. This very closely echoes a lifecourse approach in epidemiology, where the goal is to identify pathways linking exposures throughout the entire lifespan on later health outcomes. I first will review lifecourse theoretical framework. Then I will discuss this issue with regard to the area of focus of this thesis – adult social position, aerobic fitness, physical working conditions, and social interaction—in more detail.

1.2 The lifecourse paradigm in epidemiology

1.2.1 An introduction to the lifecourse approach

A lifecourse approach is a theoretical framework for guiding research on health that draws on many fields, including psychology, sociology, and biology. Central to this approach is the consideration of physical, psychological, and social exposures throughout an individual's entire lifecourse—in childhood, adolescence, and adult life—on later disease risk (Ben-Shlomo & Kuh, 2002). The lifespan approach to the study of development and health is not new; psychology and sociology have long taken this approach, ranging from Freud's claims about childhood experiences and their influence on personality development, to Elder's conceptualization of poor health as the result of a series of unfortunate events unfolding across the lifespan (Elder, 1998). Even in epidemiology, some studies in the 1950s implied the importance of considering earlier factors' effect on individual differences in health. As recounted by Pickles, Wadsworth, and Maughan (2007), this included a study showing that the negative emotional environment of orphans had an effect on growth rate (Widdowson, 1951) and another finding that childhood conditions were important in the development of adult-onset bronchitis (Reid, 1969).

Over the last three decades, epidemiological thinking about lifecourse processes has developed considerably. The shift in interest from a lifestyle approach to chronic diseases in epidemiology, to one that considered earlier exposures, stemmed in part from the use of historical cohort studies used to study early lifecourse risk factors of heart disease and other chronic diseases. Of particular importance was work related to the biological "programming" hypothesis (Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003). Building on work by Forsdahl (1977), who found that experiencing poor living conditions in childhood was an important risk factor for adult heart disease, Barker popularized the hypothesis that programming in utero increases risk of heart disease in adulthood by influencing the biological system. This hypothesis was presented as an alternative paradigm to the adult lifestyle model of adult chronic disease that focused on how behaviors influenced the risk of diseases in adulthood (Kuh et al., 2003). According to Kuh et al. (2003), these two paradigms became very polarized. The formulation of the lifecourse epidemiology framework, by Kuh and others, sprung out of a desire to unite these two hypotheses; rather than biological and social factors acting throughout life independently, the lifecourse framework posited that these risk factors act cumulatively and interactively on health and disease risk in adult life (Lynch & Davey Smith, 2004). Given its focus on social determinants of health, the lifecourse

framework thus overlaps considerably with social epidemiology, the branch of epidemiology that studies the role of social factors in health and disease in population (Oakes & Kaufman, 2006). The lifecourse framework has developed substantially over the past decade, with several books written on its historic development, theoretical framework, empirical challenges, and empirical findings. For a comprehensive presentation of the lifecourse framework, the reader is referred to the book edited by Kuh and Ben-Shlomo (2004), and for a discussion of methodological approaches, to the book edited by Wadsworth, Maughan, and Pickles (2007a). For briefer introductions, there are several excellent papers (e.g., Ben-Shlomo & Kuh, 2002; Kuh et al., 2003).

Lifecourse causal models

A central idea in the lifecourse approach is resolving which pathways link conditions earlier in life with adult health outcomes. On the broadest level, there are two conceptual models of how the timing of exposures influences health: *latency* models and *pathway* models (Wadsworth, Maughan, & Pickles, 2007b). The first of these, also known as the sensitive or critical period model, suggests that exposures during a specific developmental period have direct and enduring consequences on outcomes later in life (this corresponds to Barker’s programming hypothesis). Pathway models, in contrast, describe a process in terms of accumulation or cascades of risk. The simplest of these, the chain-of-risk model, posits that exposures early in life are primarily disadvantageous because they lead to future exposure to risk, but only later in life do the effects of the exposures become expressed as ill health. A more complex pathway model, the cumulative risk model, implies that each additional episode of adverse exposures adds to an ever-growing health disadvantage. Causal diagrams representing these three lifecourse models are presented in Figure 2, though more complex models have also been proposed—see, for instance, Kuh et al. (2003). Further, the

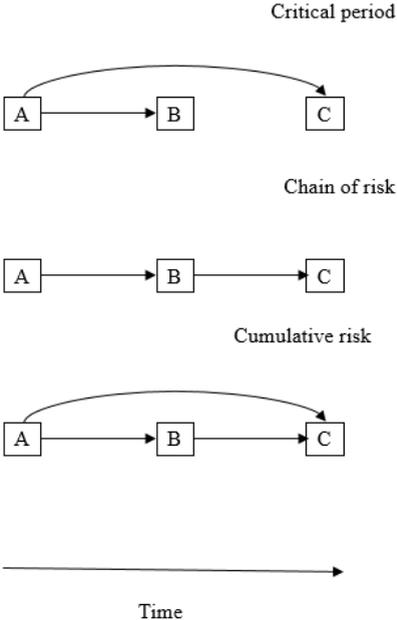


Figure 2. Alternative lifecourse models

models presented above are not necessarily mutually exclusive; rather, a combination, of them may in fact be more plausible. For instance, harsh social conditions in childhood could be particularly detrimental to health during a sensitive period, and could additionally lead to a cascade of increasing risk through the lifecourse. Several review studies on the independent effect of conditions earlier in life on adult health outcomes is persuasive (Cohen, Janicki-Deverts, Chen, & Matthews, 2010; Galobardes, Lynch, & Davey Smith, 2004, 2008; Pollitt et al., 2007).

Identifying the correct models is useful for several reasons. First of all, such models provide a framework for identifying possible exposures early in life to test in relation to later health outcomes. Second, it lays out possible pathways and mediating variables, which has important implications for interventions. If there is a critical period in early life, interventions targeting adults would be a waste of resources. On the other hand, if an accumulation-of-risk model is correct, early intervention might be best, but later intervention could also be valuable. Third, they enable the identification of possible confounding factors, which has important analytic implications. For example, if one is interested in studying the effect of an adult risk factor on later health, then if the accumulation-of-risk model is correct, ignoring the contribution of early lifecourse factors could lead to biased results. Finally, by conceptualizing the role of exposures and outcomes over time, it makes clear how the issue of “reverse causation” can hamper the analysis. Researchers have long recognized reverse causation as a threat to causal inference in observational studies of the social gradient in health. The Black Report acknowledges that at least some portion of the association between social position and health likely reflects “downward social drift” (Department of Health and Social Security, 1980). Poor mental health could lead to lower social position, and not simply be a result of it. Ignoring reverse causation would in that case lead to an overestimation of the impact of social position on mental health.

1.2.2 Early lifecourse approach in sick leave

Bäckman and Palme conducted one of the few studies that has considered sick leave in a lifecourse perspective (Bäckman & Palme, 1998). Using register data on around 15,000 individuals born in Stockholm in 1953, they tested a series of hypotheses regarding the mechanisms linking conditions in childhood and social upbringing to sick leave in adulthood under the general theoretical framework of “social heredity.” Two of the hypotheses they tested had their roots in the critical period model: the biological imprint hypothesis held that there was a sensitive period to *biological* exposures in childhood, and the social imprint

hypothesis asserted that there was a sensitive period to *sociological* exposures in childhood. The other two hypotheses they tested were linked to pathway models: the unfavorable career hypothesis posited that exposures during childhood were linked to adverse outcomes in adult life through their effect on educational and occupational trajectories, while the culture of poverty hypothesis posited that the accumulation of risk was due to a transmission of culture and values across generations. To test the various hypotheses, their general approach was to include successively “intervening variables” (i.e., mediators) in the model, and see whether an effect of the putative exposure remained once the mediating variables were included in the model. They rejected the biological imprint hypothesis outright because biological measures (birth weight and gestational age) were not significantly associated with sick leave. Similarly, they also rejected the culture of poverty hypothesis because the indicator they had used to measure norms (receiving cash benefits) did not remain significantly associated with sick leave once social conditions in childhood (paternal socioeconomic status), education, and current socioeconomic status were included. They found support for the unfavorable career hypothesis, however, based on the reduction of the effect of social conditions in childhood on sick leave once adult factors were considered. They also concluded that there is evidence of social imprint, as individuals with poor childhood (been in contact with childhood welfare services) were particularly sensitive to the effects of a low social position in adulthood.

Another study that takes a lifecourse approach to long-term sick leave is one by Henderson et al. (2012) using data from the 1958 British Birth Cohort. Their conceptual starting point was that sick leave research on occupational psychosocial risk factors does not account for earlier lifecourse factors that might be relevant to the analysis. Specifically, they argue, somatic and neurotic symptoms manifested earlier in life may confound the link between occupational risk factors and sick leave. They examined the effects of psychological distress, musculoskeletal symptoms, and low decision latitude (at age 33) on sick leave risk nine years later. They found that low decision latitude strongly predicted subsequent sick leave, and this associations remained, albeit reduced, following adjustment for psychological distress and musculoskeletal symptoms at age 33. However, after including intelligence and education in the model, low decision latitude was no longer significantly associated with sick leave. Further adjusting for early life somatic and neurotic symptoms had little impact. They conclude that low decision latitude appears to be a “downstream” risk factor. To place it in context of the lifecourse models presented earlier, one might say the findings are compatible with a cumulative risk model, where intelligence and education lead to low decision latitude and poor health outcomes, which in turn leads to sick leave risk. They also point out that

psychological distress and musculoskeletal complaints could have been a result of low decision latitude at work, suggesting that controlling for these variables might be an over-adjustment.

Further, a couple of studies from Norway have applied a lifecourse approach to the study of sick leave using a national birth cohort study of all Norwegians born between 1967 and 1976. The first of these, by Kristensen et al. (2007), set out to estimate the extent to which early social conditions and individual health were associated with musculoskeletal sick leave between 2000 and 2003, and the extent to which the associations were attributable to adult socioeconomic factors (education and income). They found that lower parental education level was associated with an increased relative risk of musculoskeletal sick leave, while the other early determinants that were included (birth weight, childhood disease, parental survival, parental disability, parental income, and maternal marital status) showed no significant relation with sick leave. Further, when including indicators of socioeconomic position (in particular education), the link between parental education and sick leave was substantially diminished. Overall, the study suggests that a substantial part of the association of parental education and sick leave was mediated through the educational attainment, though a direct effect remained. The second study used the same dataset, but included only men and instead focused on psychiatric sick leave (Kristensen et al., 2010). The study set out to disentangle the relative contribution from social causation versus indirect selection in accounting for the adult gradient in psychiatric sick leave (and other psychiatric outcomes). Results showed that parental and individual characteristics during the early lifecourse accounted for a moderate part of inequalities in psychiatric sick leave. General ability at the age of 18 years had strongest influence on the sick leave gradient. This study indicates that indirect selection explains a substantial part of social inequalities in certain psychiatric outcomes and that early life prevention is important to reduce the social gradient in sick leave.

Finally, another study by Henderson, Hotopf, and Leon (2009) explored the association between childhood temperament and long-term sick leave² in middle age. The study used data from the Aberdeen Children study initiated in the 1950s, in which teachers had rated the children on aspects of child temperament (e.g., having frequent aches and pains, appearing to

² In the article, they refer to the outcome as long-term sick leave. This outcome was obtained by self-report in response to “whether or not the respondents classified themselves as ‘permanently sick or disabled’. It thus seems somewhat unclear whether this really should be classified as long-term sick leave or as disability, though I have included it here under the sick leave section due to the way the authors themselves defined it.

be miserable, being delinquent from school). They found a strong dose-response relationship between childhood temperament and long-term sick leave in middle age, even after controlling for the father's social class (self-reported). They assessed whether education and intelligence mediated the link between childhood temperament and long-term sick leave, finding that the association was reduced when education and intelligence were included, although significant trends remained.

1.2.3 Disability pension in a lifecourse perspective

While few studies have taken a lifecourse approach in studying sick leave, the focus on early childhood conditions has received somewhat more attention in research on disability. This focus goes all the way back to 1971, when Lindén undertook a study on the association between social class in childhood and later disability pension risk in a Norwegian population (1971). In more recent years, a retrospective study found that the risk of disability pension is tied to negative childhood experiences (Harkonmäki et al., 2007), even after controlling for health-related risk behavior (i.e., smoking, alcohol consumption, obesity). A prospective study in Sweden found that conditions present or established in youth and adolescence were of major importance to understand the social gradient in sick leave (Upmark, Lundberg, Sadigh, & Bigert, 2001). Their findings suggested that the increased risks for skilled and unskilled manual workers compared with non-manual employees might be interpreted according to the concept of unfavorable life careers. Last, two studies from Norway identified several childhood biological and social background risk factors for disability pension risk in early adulthood. Gravseth et al. (2007) found that birth weight, childhood chronic disease benefits, maternal marital status, and parental disability pension were associated with increased risk of disability pension hazard. Further, they found that the effect of parental disability pension was strongest when the parent was of the same gender as the offspring. In a later study, Gravseth et al. (2008) investigated to what extent the link between early childhood conditions and disability pension in men appeared to be mediated by education and intelligence. While childhood conditions were associated with disability risk, intelligence and education had the strongest association with disability pension.

1.2.4 Lifecourse approach in current thesis

For the current thesis, I will use the lifecourse paradigm as a lens through which to see the etiology of sick leave, that is, as a process originating in early life, and developing through various biological, psychological, and social pathways. This thesis will not be testing specific pathways against one another. Rather, I will explore exposures to sick leave that are

manifested at an earlier age than what is normally studied. Second, I will include early lifecourse factors in the analysis as a way of reducing bias. Our main model for Paper I and Paper II will be that of an *unfavorable career hypothesis*. Central here will be mediation analysis, or decomposition of effects. In Paper I, we will focus on the link between aerobic fitness at age 18, and the possible mediating role of occupational and educational trajectories—that is, that aerobic fitness could impact education and occupational trajectories, which could further increase the risk of sick leave. This paper can then be said to be exploring a bio-social pathway—the way that the influence of biology possibly acts through social careers. The role of childhood conditions and other individual characteristics will primarily be included as confounders of the relation between aerobic fitness and sick leave. In Paper II, we consider adult social position and the degree to which it is mediated through physical work, while taking into consideration downstream individual and social factors. The personality trait neuroticism and social conditions during childhood and adolescence are of special interest. This approach is similar to the paper by Henderson et al. (2012), in that we are considering psychological and social pathways. This paper will apply more advanced methods in statistics that are able to deal more suitably with the challenges of lifecourse analysis. Papers III and IV, are similar in nature to the cultural hypothesis of Bäckman and Palme (1998), in that we will be considering the possibility of a social influence mechanism accounting for aggregation of sick leave amongst family members. Paper III will consider the influence of more distal exposures, namely parental sick leave during late adolescence on sick leave 15 years later. In Paper IV we consider a more contemporary exposure, sibling sick leave, though our focus is on a very specific time: the first years of employment. Further, we will use methods that are more advanced and that are able to incorporate individual propensity to sick leave into the model.

1.3 Physical fitness and sick leave

In the epidemiological literature, researchers often use the terms physical fitness and physical activity interchangeably, even though that may not always be appropriate (Caspersen, Powell, & Christenson, 1985; Ortega, Ruiz, Castillo, & Sjöström, 2008). The same appears to be true for sick leave research, where there is not always a clear delineation between aspects focusing on physical activity as opposed to physical fitness.³ Thus, some clarification seems in order. Broadly speaking, *physical fitness* refers to a set of attributes that people have or can achieve. More technically, physical fitness has been defined as “the capacity to perform physical activity, and makes reference to a full range of physiological and psychological qualities” (Ortega et al., 2008). There are several components of physical fitness, including cardiorespiratory endurance, muscular strength, muscular endurance, body composition, and flexibility (Caspersen et al., 1985). *Physical activity* is an action that can lead to better physical fitness, and is usually defined in terms of energy expenditure (Malina, 2001). However, there is not a one-to-one relation between physical activity and physical fitness, as genes also contribute to a person’s physical fitness. Further, while increasing physical activity could potentially lead to increased physical fitness, an increase in physical activity is also associated with a host of other outcomes that could potentially be linked to health.

Measuring physical activity objectively is much more challenging than measuring physical fitness. Generally, the former is measured by self-report, whereas the latter is measured using more objective tests (e.g., ergometer test). This might tend to make studies measuring physical fitness less prone to bias, and it has therefore been argued that measurements of physical fitness are preferable to physical activity when studying risk factors for sick leave (Amlani & Munir, 2014). In the sick leave literature, the focus of the vast majority of studies is on physical activity rather than physical fitness. As such, while the focus of the current study is physical fitness—specially, aerobic fitness, one of the components of physical fitness—I will review the literature on physical activity and sick leave as well, given its link to physical fitness.

³ An example of this is the literature review by Amlani and Munir (Amlani & Munir, 2014), in which they, judging by the title and abstract, review evidence of an association between physical activity and sick leave. However, their review is not limited to studies merely focusing on physical activity but also includes papers where physical fitness is the main exposure variable.

1.3.1 Literature on the impact of physical fitness and physical activity on sick leave

The relation between physical activity and sick leave has been a topic of great interest in the sick leave literature, while just a few studies have focused on physical fitness. The methodological approaches used in both cases can broadly be grouped into two categories: *observational studies*, where the association between either physical activity or physical fitness and sick leave have been assessed using either cross-sectional or longitudinal prospective data, and *intervention studies*, where a treatment group has been assigned an intervention consisting of physical activity. For a thorough literature review, see the papers by Proper, Staal, Hildebrandt, Van der Beek, and van Mechelen (2002), who focused on intervention studies, and Amlani and Munir (2014), who considered both observational and intervention studies.⁴ I will here briefly review some of the findings and discuss some of the methodological issues that could potentially have biased the results.

Though cross-sectional studies do not provide much evidence in favor of a causal link between an exposure and sick leave, one of the earliest studies assessing a link between physical fitness and sick leave was cross-sectional. In the 1960s, Lindén studied the association between physical fitness (specifically, cardiovascular fitness) and sick leave (1969) amongst a group of firefighters and customs officers in Norway. He found that poor aerobic fitness was associated with a higher risk of sick leave amongst the latter group, but not the former. In Finland, Kyröläinen et al., studied the association between physical fitness and sick leave amongst military recruits (2008), finding a weak association. Several cross-sectional studies on physical activity and sick leave have found evidence in support of an association; all of the eight cross-sectional studies reviewed by Amlani and Munir (Amlani & Munir, 2014) found a positive association between physical activity and sick leave (though not for all levels of intensity of physical activity).

The review by Amlani and Munir identified 11 prospective cohort studies, 10 of which had assessed the link between physical activity and sick leave, and one that had studied physical fitness and sick leave (2014). Of the studies assessing the link between physical

⁴ As an aside, it is interesting to note that although Paper I in my opinion ought to have been included in this review, it was not. The reason appears to be that they only included studies that included words related to “workplace setting” in the title or in keywords. They do not provide any further definition of what was meant by this, so it is somewhat unclear exactly what types of studies they were trying to exclude. Arguably, all studies relating to sick leave are by definition related to a workplace setting. One possible interpretation could be that they only wanted to use studies where employee data were obtained from the workplace, or that physical activity was measured at the workplace. However, neither of these are consistent with the papers that are included in the study.

activity and sick leave, the vast majority found a positive association, even after the confounders had been controlled for (Eriksen & Bruusgaard, 2002; Lahti et al., 2010b; Lahti, Lahelma, & Rahkonen, 2012; Proper, van den Heuvel, De Vroome, Hildebrandt, & Van der Beek, 2006; van Amelsvoort, Spigt, Swaen, & Kant, 2006; van den Heuvel, Boshuizen, et al., 2005), though not all (Christensen, Lund, Labriola, Bültmann, & Villadsen, 2007). One study found a positive association for recreational exercise, but an inverse association for work-related exercise (which was defined as strenuous work) (Holtermann, Hansen, Burr, Sjøgaard, & Sjøgaard, 2012). The study population in most of the studies were young to middle aged workers (age ranging from 37 to 60 years), and the study design was mostly to assess a measure of physical activity and other covariates at baseline, and then follow up the participants for a given amount of time (from 1.5 to 8 years).

The general modeling approach in the studies that were reviewed by Amlani and Munir was to control for a given set of putative confounders and mediators, such as BMI (Christensen et al., 2007; Holtermann et al., 2012; Lahti et al., 2010b, 2012; Strijk et al., 2011), social position (Christensen et al., 2007; Eriksen & Bruusgaard, 2002; Lahti, Laaksonen, Lahelma, & Rahkonen, 2010a; Lahti et al., 2012), work-related factors (Christensen et al., 2007; Eriksen & Bruusgaard, 2002; Holtermann et al., 2012; Strijk et al., 2011; van den Heuvel, Boshuizen, et al., 2005), lifestyle factors (Christensen et al., 2007; Eriksen & Bruusgaard, 2002; Holtermann et al., 2012; Lahti et al., 2010b, 2012; Strijk et al., 2011; van den Heuvel, Heinrich, Jans, van der Beek, & Bongers, 2005), and health status (Christensen et al., 2007; Holtermann et al., 2012; Lahti et al., 2010b, 2012; Strijk et al., 2011).

While longitudinal studies provide better evidence of a causal association between sick leave and physical activity or physical fitness, as the temporal order of the exposure and the outcome is accounted for, there are still some issues that could impede causal inference. For one, there are still likely to be confounders that were not included. Further, in nearly all cases, the confounders and mediators were all measured at the same time, and their roles either as confounders or mediators were not always made explicit. This makes it difficult to fully disentangle the relation between sick leave and physical fitness or physical activity, and their possible relation through social position or work factors.

Evidence from randomized intervention studies do not provide much evidence in support of physical activity reducing sick leave risk (Amlani & Munir, 2014; Proper et al., 2002). Of the nine trials (where assignment to treatment was randomized, and the other group received no treatment), only two of the identified studies showed that intervention reduced sick leave.

A randomized control trial from Norway (Brox & Frøystein, 2005) found that sick leave actually increased in both the exercise and control group. Intervention studies with less stringent design (e.g., in which physical activity is one of many aspects of the intervention) find slightly more evidence in support of an effect of physical activity on sick leave.

However, a number of methodological concerns, including lack of description of the physical activity program in intervention studies and use of self-report physical activity also call these results into question (Amlani & Munir, 2014). They conclude that overall that “the available evidence provides limited support that physical activity is effective in reducing sickness absence, due to the low quality of many of these studies.”

1.3.2 Physical fitness in a lifecourse perspective

Although many of the negative health outcomes linked to poor physical fitness and poor physical activity are not manifested before adulthood, researchers are increasingly aware that their development may start already in childhood and adolescence (Hallal, Victora, Azevedo, & Wells, 2006). Consequently, public health officials have recommended physical activity for children and adolescents (Haskell et al., 2007; World Health Organization, 2010). However, the evidence of a link between physical activity and adult health is a bit mixed. A review study concluded that there is generally low to moderate relationships between childhood and adolescent physical activity and health and adult physical activity and health (Malina, 2001). Using data from two of the British birth cohorts, Sacker and Cable (2006) studied the association between physical activity in adolescence and self-assessed health 15 years later. While there was clear association in the 1958 cohort, there was no significant association in the 1970 cohort. A 15-year longitudinal study from the Netherlands found that aspects of physical fitness and physical activity in adolescence were predictive of the development of bone mass of individuals at age 28 (Kemper et al., 2000).

While physical activity, and to some extent physical fitness, in childhood and adolescence have been studied in relation to a wide array of health outcomes, to my knowledge, sick leave has received very little attention. In a lifecourse perspective, one might imagine that to the extent that physical fitness does have a causal influence on sick leave, it could exert its influence on sick leave starting at an earlier stage in life. Further, poor physical fitness early in life could lead to a cascade of detrimental outcomes. One such possible pathway is through education and occupational trajectory.

1.4 Pathway from socioeconomic position to sick leave through physical workload

It is a near universal truth that individuals with low socioeconomic position are worse off on nearly all measures of health and mortality (Marmot, Allen, Bell, Bloomer, & Goldblatt, 2012; Marmot, 2005). The same pattern has been found for sick leave in a wide range of cross-sectional and longitudinal studies (Allebeck & Mastekaasa, 2004b). Several mechanisms linking socioeconomic position to sick leave appear to account for part of the social gradient in sick leave, including physical and psychosocial work factors, and a range of lifestyle factors. In reviewing the papers on a social gradient in sick leave, Allebeck and Mastekaasa (2004b) conclude that, despite the number of publications, the foundation for making any causal inferences is scant, a conclusion that has been drawn by others in more recent commentaries on the literature (Hoven & Siegrist, 2013; Kristensen & Aalen, 2013). Part of the reason why causal inference is difficult is that the link between socioeconomic position and sick leave is confounded by early lifecourse factors. As is well known, it is not random who is selected into higher social position, and who gets the better jobs (Deary et al., 2005). As seen in Figure 3, Model A, unmeasured early lifecourse factors (C) could confound the relation between socioeconomic position (E), working conditions (M), and sick leave (D).

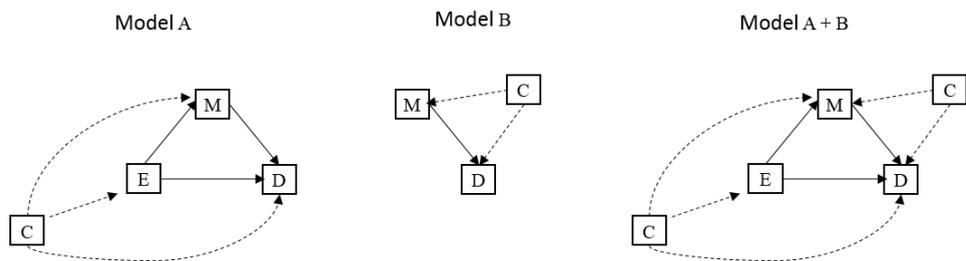


Figure 3. Causal diagrams showing possible confounded pathways

However, as reviewed in the previous section, early life confounders are rarely included in mediation analyses linking socioeconomic position and sick leave. Many early lifecourse factors would, of course, be of interest, in particular health; the availability of health data from the registries relevant to earlier stages of the lifecourse is, however, rather limited. Instead, I shall consider the role of childhood and adolescent social position and the personality trait neuroticism. The role of personality characteristics has, to my knowledge, not been considered in mediation studies linking socioeconomic position to sick leave. This omission is somewhat strange, as personality has been important in two relevant areas. First,

it is increasingly seen as an important factor in lifecourse studies as a mechanism accounting for the relation between socioeconomic position and health. Second, as depicted in Model B, the personality trait neuroticism (C), or emotional instability, is often considered in studies on the effect of working conditions (M) on sick leave (D) as a source of bias (and, though not depicted as such here, has also been considered as an independent risk factor and as a moderator of work-related factors). These two fields of inquiry have independently focused on pathways that are actually linked in a greater causal network, as shown in Model A + B. By considering these factors simultaneously, we are able to reduce a source of potential bias in the analysis of the social gradient in sick leave, and the mediating role through work factors.

In this section, I will first review the literature on socioeconomic position and sick leave and the mediating role of work. The confounding role of childhood and adolescent social position were presented in greater detail in section 1.2, and will not be presented here. Instead, I shall introduce personality and its link to health and sick leave, followed by evidence from lifecourse research on the role of personality in the social gradient in health (Figure 3, Model A), and finally present occupational research on the role of neuroticism (Figure 3, Model B).

1.4.1 Past research on socioeconomic position and the mediating role of work conditions

To my knowledge, six longitudinal cohort studies have examined whether various work-related factors explain the socioeconomic gradient in sick leave. The studies used the general analytic approach of first fitting a model adjusted for various demographic factors and confounders, and then adding the putative mediating variables to see how much the association was reduced.

North et al. (1993) studied the socioeconomic gradient in sick leave in Britain (using data from the Whitehall II study). They found strong social gradients for both short- and long-term sick leave, with higher sick leave rates among employees with low socioeconomic position. They assessed whether a wide array of variables could account for the gradient, including: psychosocial working conditions, job satisfaction, adverse social circumstances, self-rated health problems (in the past 12 months) and lifestyle factors. As far as I know, they were the only group to control for earlier lifecourse factors – controlling for father's occupation. The variables were all controlled for simultaneously, which reduced the gradient in sick leave by one third.

Melchior et al. (2005) studied the socioeconomic gradient in sick leave in a French employee sample (the GAZEL study). After adjusting for age, demographic characteristics, lifestyle factors, and stressful life events, employees in the lowest socioeconomic position had a risk of sick leave that was roughly three times higher than that of those with the highest socioeconomic position. Adjusting for all working conditions (both physical factors and job stress measures) simultaneously reduced the socioeconomic gradient in all-cause sick leave absence by 16% in men and 25% in women. They also did a sensitivity analysis, restricting the analysis to those who had not reported sick leave during the past year, finding that the associations were weaker among the healthier participants than among the full sample.

Christensen et al. (2008) studied the socioeconomic gradient in sick leave using a representative Danish study, controlling for physical and psychosocial working conditions, lifestyle factors, and demographic factors. A strong gradient in sick leave rate for episodes longer than eight weeks was found. Adjusting for lifestyle factors attenuated the association by 5–18%, while additional adjustment for physical working conditions reduced the association by 21–44%. Further adjustment for psychosocial working conditions had a minor effect in women only.

Sterud and Johannessen (2014) studied socioeconomic gradient in nationally representative Norwegian sample. They included work-related mechanical and psychosocial factors, self-reported health, and lifestyle factors. A strong socioeconomic gradient was found for a sick leave period of 40 or more days, adjusting for age and region. Adjusting for mechanical factors only resulted in 15-32% reduction for men, and 23-39% reduction for women, while adjusting for psychosocial factors only resulted in 21-33% reduction for men and 22-33% reduction for women. The combined impact of mechanical and psychosocial work-related factors on the socioeconomic gradient ranged from 41-44% reduction among men and 31-54% reduction among women.

Kaikkonen, Härkänen, Rahkonen, Gould, and Koskinen (2015) studied the socioeconomic gradient in sick leave using a nationally representative sample from Finland. They controlled for psychosocial working conditions, physical working conditions (demanding work, chemical hazards), lifestyle factors, health measures, work ability and demographic factors. Their results suggest that improvements in physical working conditions and reduced smoking may lead to a reduction in educational gradient in sick leave.

In a methods paper, Lange and Hansen (2011) presented a novel way of doing a mediation analysis for survival data. The method developed in their paper is the foundation for the analysis used in Paper II, and will be discussed in more detail in section 3.6.2. They

reanalyzed data from the study by Christensen et al. (2008), but only included the physical working conditions and demographic factors in the model. Their results were qualitatively in line with the findings by Christensen et al., showing that a reduction of physical workload in the lowest social group to the level of those in the highest social group would lead to 39% fewer sick leave episodes among women, and 43% fewer episodes among men.

To summarize the findings, studies varied in terms of which work factors they included, though those that included both physical and psychosocial factors found that physical factors accounted for most of the gradient in sick leave (Christensen et al., 2008; Kaikkonen et al., 2015; Melchior et al., 2005; Sterud & Johannessen, 2014). Further, in all studies, a large part of the social gradient remained unexplained even after accounting for a wide range of factors (e.g. baseline physical health, demographic factors, and lifestyle factors). One possible explanation for this is, of course, that the effect of socioeconomic position on sick leave is acting through other unmeasured pathways. Another possibility, however, is that the estimates between socioeconomic position and sick leave are overestimated due to unmeasured confounders. The study by North et al. (North et al., 1993), did include social class of the father, though this was self-reported, and could be a poor indicator of overall conditions during the early lifecourse.

When seen as a whole, the evidence of a causal association is indeed somewhat limited. First, there is the issue of not controlling for earlier social conditions. In addition, the practice of controlling for health conditions at baseline, which was done in all the studies except for that by Lange and Hansen (2011), is perhaps somewhat questionable. The main reason for including work factors as a mediator between socioeconomic position and sick leave is, of course, the belief that work factors could be detrimental for health, and increase the risk of sick leave. Arguably, at the start of follow-up, health status will reflect exposure to hazardous working conditions that have been experienced up until that point. By controlling for baseline health, one would be blocking all effects of work factors that had accumulated up until that point. Third, all studies referenced here used self-report measures of both physical and psychosocial working conditions, which the authors pointed out could have given rise to a self-report bias. Lastly, another issue, which weakens causal inference, is the analytic approaches that were used in the studies: with the exception of the study by Sterud and Johannessen (2014), who fit a logistic model, all the studies fit Poisson regression models (Christensen et al., 2008; Kaikkonen et al., 2015; Melchior et al., 2005; North et al., 1993). As pointed out in Lange and Hansen, these mediation approaches for non-linear models do not lead to results that are interpretable in a meaningful way.

1.4.2 Personality—some background

Definition

Personality refers to several stable traits with respect to behavior, affect, interpersonal interactions, and cognitive dispositions (Lahey, 2009). In the literature, there is now a consensus that people differ on five major dimensions of personality: neuroticism, extraversion, conscientiousness, agreeableness, and openness to experience (Matthews, Deary, & Whiteman, 2003). For a detailed guide to personality see the book by Matthews et al. (2003). The five main traits, or the Big Five, can be summarized as follows (Costa & McCrae, 1992): *Neuroticism* is the tendency to feel anxiety and other negative emotions versus a tendency to be calm and emotionally stable. *Extraversion* is the tendency to be social, outgoing and to prefer being around people, as opposed to a tendency to prefer being alone, and being more reserved and serious. *Conscientiousness* is the tendency to be dutiful and organized versus being somewhat careless and disorganized. *Agreeableness* is the tendency to be trusting and deferential as opposed to stubborn and independent. *Openness to experience* is defined as being open to new ideas and feelings as opposed to being narrow-minded and shallow. Each of the personality traits are comprised of scores on six facets that are generally measured using separate scales. For instance, the facets making up neuroticism are: anxiety, hostility, depression, self-consciousness, impulsiveness and vulnerability (Costa & McCrae, 1992).

Generally, personality has been thought to be determined at birth and to remain fixed throughout lifetime. McCrae and Costa's (1996) five-factor theory asserts that personality traits are fully determined by genes and that they reach full maturity in early adulthood. However, recent evidence has challenged this perspective, which has led some to argue that traits are determined not only by genes, but also the individual's social environment (Poulton et al., 2002). Although personality could, in part, be a result of individual experiences, a recent literature review summarizing previous studies of mean-level change on the Big Five (Roberts, Walton, & Viechtbauer, 2006) suggests that such changes would be rather small.

Personality, health, and sick leave

Considerable research has shown that personality traits and health are interrelated (Smith & MacKenzie, 2006). One large area has focused on the link between Type A personality (related to lower agreeableness and to higher neuroticism), which is strongly predictive of coronary heart disease and mortality (Smith & MacKenzie, 2006). A strong case has been made that neuroticism in particular "is a psychological trait of profound public health

significance” (Lahey, 2009). In reviewing the link between neuroticism and health outcomes, Lahey concludes that neuroticism is a robust predictor of many different mental and physical disorders and the frequency of use of mental and general health service. Further, it appears to be correlated with a wider range of mental and physical health problems than other personality traits. This includes many Axis I and II mental disorders through the lifecourse (e.g. personality disorders and major depressive episodes). Given the extensive association between sick leave and health, one would expect personality to play an important role for sick leave as well.

Some research points to an association between some aspects of personality and sick leave, though few studies have looked specifically at the Big Five personality traits. Vlasveld et al. (2013) found that high neuroticism, external locus of control, low extraversion, low agreeableness and low conscientiousness were associated with short-term sick leave. In addition, high neuroticism, low extraversion and low openness were related to long-term sick leave. Störmer and Fahr (2013) studied the relation between the Big Five personality traits and sick leave, finding a clear negative correlation between sick leave and conscientiousness among women. For male employees, low agreeableness predicted a higher incidence of sick leave. When looking at the length of the sick leave episode, neuroticism was found to significantly influence male sick leave, even after controlling for subjective health. Thus, while neuroticism does not appear to be the only personality trait relevant for sick leave, it does seem to play a role, especially for sick leave episodes of longer duration.

1.4.3 Personality as an early lifecourse confounder

In addition to the strong link between personality and health outcomes, personality is also linked to social conditions throughout the lifecourse (Poulton et al., 2002). There is a greater prevalence of negative personality patterns (e.g. high neuroticism) and unfavorable coping styles among those raised in lower social position (Bosma, van de Mheen, & Mackenbach, 1999; Jonassaint, Siegler, Barefoot, Edwards, & Williams, 2011), and certain personality traits are predictive of adult socioeconomic attainment (Miller, Kohn, & Schooler, 1986). Given the link between socioeconomic position and health, and personality and health, some have argued that personality could be central in accounting for the social gradient in health (Gallo & Matthews, 2003; Krueger, Caspi, & Moffitt, 2000; Poulton & Caspi, 2003).

A review of the possible mechanisms is presented by Krueger et al. (2000). One area of focus has been on psychobiological pathways, which suggests that certain personality traits make people more biologically reactive to poor conditions. Other accounts view personality

more as a background determinant of both adult socioeconomic positions and health, or health related behavior, that is, as a contributor to socioeconomic differences in adult health outcomes. This was the framework for the study by Henderson et al. (2012), who studied whether temperament in childhood accounted for the relation between work conditions and sick leave in adult age. Their findings suggested that childhood temperament was predictive of sick leave, though this effect was negligible after education, intelligence, and working conditions were taken into account. Similarly, Pulkki et al. (2003) investigated the extent to which type A personality in adolescence and early adulthood accounted for the link between education and behavioral cardiovascular disease risk factors in adulthood. They concluded that the association between adulthood education and smoking in men and women and physical inactivity in women may be partly rooted in personality-related factors present earlier in life. Similarly, Hampson, Goldberg, Vogt, and Dubanoski (2007) found that childhood personality traits confounded the link between educational attainment and health behaviors. Childhood agreeableness, conscientiousness, and openness influenced adult health status, were in part acting indirectly through educational attainment, healthy eating habits, and smoking.

There is also substantial evidence to support that personality is linked not only to educational attainment, but to work outcomes. In a review of the relative strength of personality and social position on later life outcomes, including unemployment, Roberts, Kuncel, Shiner, Caspi, and Goldberg (2007) conclude that “It is abundantly clear from this review that specific personality traits predict important life outcomes, such as mortality, divorce, and success in work, even when controlling for SEP”. Others have shown that personality traits are predictive of occupational choice (Barrick & Mount, 2005; Judge, Higgins, Thoresen, & Barrick, 1999; Ozer & Benet-Martínez, 2006) and subsequent job performance (Judge et al., 1999).

1.4.4 Neuroticism in the occupational literature

Neuroticism has been an area of wide interest in the work environment literature. For an in-depth discussion, see the article by Spector, Zapf, Chen, and Frese (Spector, Zapf, Chen, & Frese, 2000) or the book by Wainwright and Calnan (2002). Individuals high on neuroticism tend to report more adverse working conditions (Spector et al., 2000), including higher physical workload (Rolander, Stenström, & Jonker, 2008). One viewpoint is that this reporting pattern is the result of a bias, as opposed to an objective categorization of the work environment (Rolander et al., 2008). This would suggest that, unless one controls for

neuroticism, one would be overestimating the effect of report of hazardous work conditions on sick leave. This concern has mostly been in regards to psychosocial work aspects, not the report of physical workload. Nonetheless, the same link between neuroticism and physical working conditions has been found (Rolander et al., 2008), and there seems little reason to doubt that the same personality characteristics that would make someone “over-report” a negative psychosocial environment would also be in operation in the reporting of how heavy physical work environment is experienced.

The other viewpoint holds that one should not control out this reporting pattern, because what we are interested in measuring is how a person perceived a given environment, not how someone else might perceive it. That is, individuals who are high on neuroticism will actually experience a given set of working conditions—be they physical or psychosocial—as more hazardous, and as such it would be wrong to “control” for this. The basic theory is that an underlying “vulnerability” makes people more at risk for a given environment, and that we should identify these cases.

Regardless of which viewpoint one takes, it is clear that neuroticism could play an important role in the analysis of work factors as a mediator between the socioeconomic gradient and sick leave. If neuroticism is an effect modifier of the relation between working conditions and sick leave, then one should account for that in the model. If, on the other hand, it represents a confounder, then it should be controlled for.

1.5 Social interaction

Until now, I have considered the unfavorable career hypothesis, focusing on how physiological factors (Paper I) and social conditions (Paper II) are linked to sick leave through an education and work-related trajectory, while taking into account early lifecourse conditions. This section focuses on another possible mechanism of how conditions in early lifecourse could be influencing later sick leave risk: through familial social influence, or social interaction, from parent to offspring, and from older to younger siblings. The concept of social interaction as an account of sick leave risk has gained recent attention in sick leave research. The interest in a social influence has sprung out of the inability of known risk factors, like socioeconomic factors and health conditions, to account for the individual variance in sick leave risk. While at the same time, there are patterns of sick leave fluctuations over time and clustering of risk in geographical regions and within families. Social interaction has also been invoked as a possible explanation for why the sick leave risk has increased among women. The bulk of studies have looked at social interaction effects in more distal

peer groups—neighbors and colleagues, with very few considering the role of family members. However, family members are arguably more important for the formation of the underlying psychological processes that could influence sick leave behavior, such as norm formation and health beliefs. Here, I will present an introduction to the concept of social interaction, followed by a review of sick leave research in this field, and lastly, motivations for considering parental and sibling effects.

1.5.1 Some background on social interaction

The idea that we, as individuals, are influenced by the behavior of those around us has been very central in psychology, going back to Bandura (1977) and Festinger (1954). More recently, this has been introduced as a topic of great interest in epidemiology, though here the interest has been on identifying contextual, or neighborhood effects.⁵ What I refer to as social interaction, is then meant to be the process by which humans influence someone else to change their thought or behavior pattern. It might, on some level, seem strange to view sick leave as determined by social influence, as sick leave is in part illness due to having poor health. But, in the sick leave process, there are many steps that could potentially be influenced by others. When does a person feel ill? When does a person decide to go to a doctor? These processes determine whether a person will go on sick leave, and the choices a person makes could in part be due to the behavior and influence of others. One could be influenced in terms of learning more about the sick leave system, about going to the doctor, or the influence could be more closely related to beliefs and norms.

Social interaction is, however, notoriously difficult to measure. Credible approaches involve control for observable and unobservable confounders, and to tackle the innate reflection problem in the relationship between the group and the individual. These issues are outlined by Manski (1993). A variety of approaches have been taken to deal with this in the sick leave literature, which I will briefly review.

1.5.2 A review of social interaction in the sick leave literature

Several studies have explored whether sick leave is in part attributable to social interaction effects. The bulk of the literature has focused on social interaction effects between neighbors

⁵ Depending on the literature, social influence has been referred to by a wide variety of names, including “peer influences,” “neighborhood effects,” “contextual effects,” “social capital”, “network analysis”, while not all the literature is always clear in terms of what exactly is being measured (Manski, 1993).

and colleagues. To my knowledge, only two studies have considered possible social interaction effects of sick leave among family members. Markussen and Røed (2015) assessed whether social interaction within neighborhoods and families could account for sick leave and other types of absence from work (e.g., disability pension) by using a fixed effects methodology. They defined different constellations of family members according to degree of relatedness, including one consisting of siblings and parents, and another consisting of uncles, aunts, and cousins. As a measure of social interaction, they estimated whether an increase in the probability of sick leave within one of these family constellations increased the hazard of sick leave, and whether this effect was stronger with increasing relatedness of family members in the constellations (i.e., whether sick leave among the sibling-parent group increased sick leave hazard more than sick leave among aunts, uncles and cousins). They found a moderate social interaction effect, which was weaker the more distantly related the family members were. However, as they mention, they did not take into account family propensity to sick leave, which means that it is difficult to rule out whether the similarities in sick leave hazards among family members were caused by a shared genetic propensity to sick leave. Further, their study did not distinguish between parental versus sibling exposure. Another study, by Gjerde et al. (2013) used a twin design to assess whether there was a social interaction effect amongst sets of twins, but did not find evidence in support of that. However, the approach used does not have much power to detect possible interaction effects (Gjerde, 2014).

Several researchers have studied social interaction effects among colleagues and neighbors, using the approach of seeing how a person's sick leave behavior changes once he or she moves to a new workplace in which the sick leave propensity differed from the prior workplace. Ichino and Maggi (2000) studied bank employees in Italy who move between a Northern and Southern branch. The authors found that after moving, the employee adapted to the average sick leave level of the colleagues at the arriving branch. Bokenblom and Ekblad (2007) used Swedish employment records at 413 work places to analyze social interaction effects among colleagues. They found a positive and significant group effect. Further, they found that on average, it took two to three years for a new employee to adopt the pattern of the work group. Another interesting finding was that the peer effect is mainly evident within gender, and within age group. That is, men influenced other men, and women influenced other women, but men and women did not influence one another. Lindbeck, Palme, and Persson (2008) use a variety of approaches, and in one instance study the impact on sick leave behavior of moving between different neighborhoods. They take advantage of the fact that the

sick leave rate of people in the public sector is higher than for people in the private sector, and use this as an instrument to assess whether employees tend to adapt to the sick leave level in the new neighborhood. They found that the proportion of public sector workers in a neighborhood to a strong extent accounts for the mean sick leave level. Their interpretation of this as a social interaction effect, rests on there being no other factors that would make people move to a certain neighborhood, an assumption that seems to be a bit of a stretch. Rieck, and Vaage (2012) compared sick leave behavior among teachers who moved between schools, testing whether a change in sick leave can be explained by the change in the level of the teachers' co-workers' sick leave. They found that their results critically depends on whether or not they are able to control for unobserved school characteristics. In models not accounting for this, there are significant social interaction effects, but in fixed effects models, where school effects are controlled for, the interaction effect is no longer measurable.

Several studies on social interaction have taken advantage of a natural experiment conducted in a Swedish municipality. The social insurance board in Gothenburg randomly assigned individuals (based on date of birth) to require less monitoring before having to obtain a physician's diagnosis (instead of the normal 7, they had 14 days of self-reported sick leave). Hesselius et al. (2008) use this natural experiment in order to identify social interaction effects among neighbors. They find that an increase of 10% among the group with less monitoring, would lead to a 6% increase in sick leave among neighbors with normal monitoring, due to social interaction. Hesselius et al. (2009) also employ this natural experiment to see how the individuals randomized to less observation influence the sick leave behavior among their colleagues. They find that sick leave days increase by 0.88 days per person among people assigned to less monitoring, while the sick leave of colleagues increase by 0.55 days, on average. This is a relatively large effect considering the mean sick leave was 2.33 days prior to the experiment. Johansson, Karimi and Nilsson (2014) employ the natural experiment to assess whether workers with less monitoring increased their absence as a response. They find an increase in sick leave among those who work with colleagues who have less monitoring. Moreover, their results suggest significant heterogeneity in the degree of influence that male and female workers exert on each other: men are only affected by their male peers, and women are only affected by their female peers.

1.5.3 Evidence of importance of parents

Overall, there is very little evidence of a possible interaction effect for sick leave propensity across generations. To my knowledge, the only study that assessed the impact of parental

work absence behavior (which included, but was not limited to sick leave), was the study by Markussen and Røed (2015). However, as outlined previously, they did not distinguish influence from parents from influence from siblings. On the other hand, intergenerational transmission in disability pension has received slightly more attention. Dahl, Kostøl, and Mogstad (2013) used an instrumental variable approach, where the instrument was the random variation in judge assignment of appeal cases for denied disability pension. They restrict the sample to offspring who are age-eligible for disability pension (at least 18 years old) at the time of the parent's appeal decision. They find that when a parent is granted disability pension due to having been assigned a lenient judge, the offspring's rate of being granted disability pension increases by 6 percentage points over the next five years. Further, they find that the intergenerational transmission amplifies over time: participation rate reaches 12 percentage points ten years after the judge's decision. Bratberg et al. (2012) assess the probability of children receiving disability pension when one of the parents has received disability pension. They find that the duration of time that the children have been exposed to their father receiving disability pension, increases their own likelihood of receiving disability pension. Lastly, Gravseth et al. (2007) find that disability pension risk increases if one was exposed to a parent who received disability pension, and this effect is particularly prominent within same-sex parent-offspring constellations.

1.5.4 Importance of siblings

While the evidence for a social interaction in sick leave behavior among siblings is slim, evidence from other lines of research suggests siblings may be important for many types of behaviors. The influence of an older sibling has been studied with respect to smoking (Bricker et al., 2006; Rajan et al., 2003), drinking (Duncan, Duncan, & Hops, 1996; McGue, Sharma, & Benson, 1996), health risk behavior (D'Amico & Fromme, 1997), and childbirth (Monstad, Propper, & Salvanes, 2011; Rosenzweig & Wolpin, 1995). Several of the studies that compared the impact from a parent, versus an older sibling, found that overall the older sibling increased risk of drinking more than the parent did (Duncan et al., 1996; McGue et al., 1996), while for smoking, parent and older sibling mattered equally (Bricker et al., 2006).

Developmentally, then, an older sibling is important for choices. In relation to sick leave, a sibling may provide a strong model of behavior (Bandura, 1977) or serve as a source of comparison (Festinger, 1954) for a younger sibling in areas that are relevant for sick leave risk, especially during late adolescence and early adulthood. For instance, a sibling may influence how physical symptoms are interpreted (Litman, 1974), whether treatment is sought

(Suls, Martin, & Leventhal, 1997), and how an illness is coped with (Giri, Poole, Nightingale, & Robertson, 2009). All of these processes could all play a role in sick leave behavior (Brooks, McCluskey, King, & Burton, 2013).

2 RESEARCH AIMS

Paper I

To investigate whether aerobic fitness in males aged from 18 to 19 is associated with their hazard of musculoskeletal sick leave 5 to 15 years later. We further assess how much of this association appears to be mediated through attained educational level and work-related factors.

Paper II

To estimate, using causal mediation analysis, the extent to which the adult social gradient in sick leave hazard is mediated through physical workload while taking into account personality and childhood and adolescent social position.

Paper III

To estimate the association between exposure to parental sick leave at age 18 and the one-year risk of sick leave 15 years later, exploring whether an association between parent and offspring sick leave is stronger on an additive scale for women than for men.

Paper IV

In this study, rather than studying parent-offspring associations, we focus on an older-younger sibling constellation. Our specific aim was to examine, using a dynamic recurrent event survival model, whether exposure to an older sibling's sick leave is followed by an increase in sick leave rate and to account for individual frailty using a dynamic covariate of past sick leave history.

3 MATERIALS AND METHODS

The papers presented in this thesis use four different study samples that all derive from the same source population based on specific eligibility criteria. I will first describe the source population, which was a birth cohort study of all Norwegians born between 1967 and 1976, and the data obtainment and linkage procedures, followed by a description of the eligibility criteria for the four samples. Most of the data have been collected from national registers. We also included data from the HUNT3 study in Paper II.

3.1 Norwegian Birth Cohort Study, 1967–1976

The source population for our research is all 626,928 individuals (321,975 males and 304,953 females) born alive in Norway from 1967 to 1976, who were registered in the Medical Birth Registry. All health personnel in Norway are required to submit a notification of birth to this registry, and coverage has been found to be nearly perfect (Hammer, 2002). Each registered individual is assigned an identification number, and the identification numbers of both parents are also included in the registry. Information about mother's identification was missing for six individuals, while father's identification number was missing for 7.1% of the individuals. We have linked families together, enabling us to identify a variety of family units, such as mother-offspring, father-offspring, and maternal siblings. Data on this population, and their parents, have been obtained from several national registers, based on the identification numbers, so that we have annually updated individual information from 1967 through 2009. I describe these sources in more detail below.

3.2 Data sources

3.2.1 National registers

Data sources and a timeline of the time periods the data covers are displayed in Figure 4. Data obtained from sources shown in grey have been measured at one time point for each individual, while data from sources in blue have been updated on an annual basis (or more frequently as event histories). Education history and educational attainment is registered in the *National Education Database* (Statistics Norway, 2003). The *Norwegian Labor and Welfare Administration* records information on sick leave diagnoses and disability pension. The *Central Population Register* registers demographic information. The event history database *FD-Trygd* (Akselsen, Lien, & Sivertstøl, 2007) compiles information from several sources from 1992 onwards, and includes information on sick leave benefits and employment

status, in addition to demographic information (including marital status, number of children). The *Medical Birth Registry* (Irgens, 2000) is a register for all births in Norway, which contains information on pregnancy and birth outcomes as well as some maternal information. Routine registration of conscription board examinations, including aerobic fitness, intelligence, physical fitness, weight and height was obtained from the *National Conscripts Service* for men conscripted to the military. These national registers were also linked to data from the HUNT3 study, which is described in the next section.

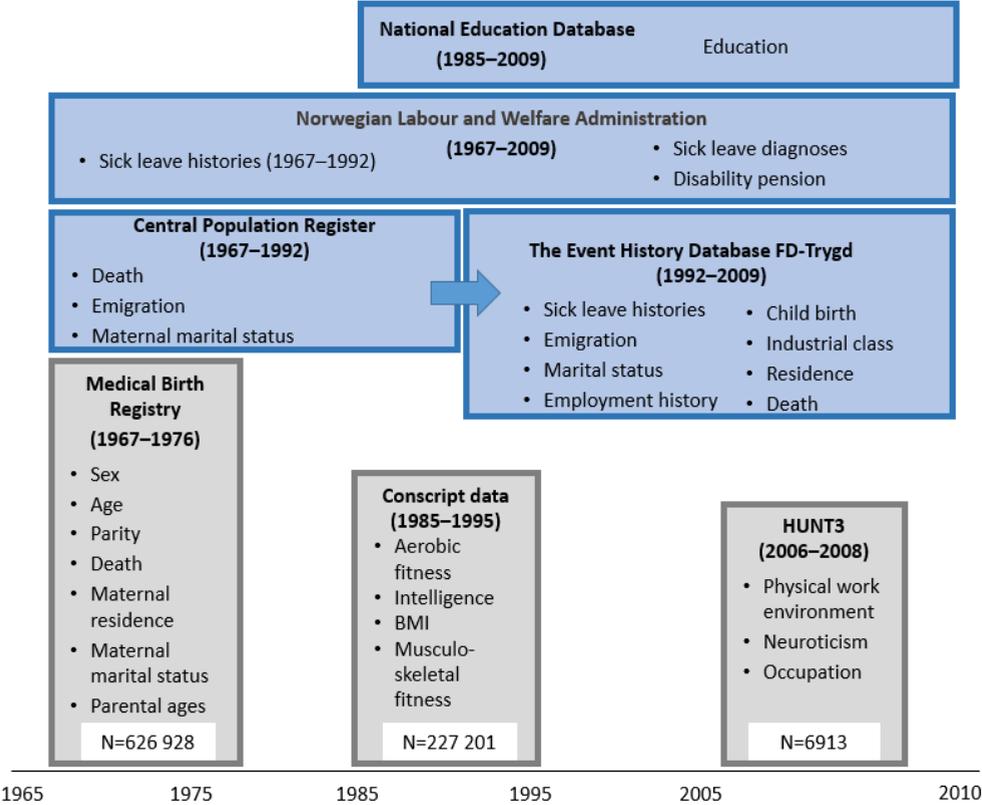


Figure 4. Data sources, range of coverage, and number of individuals included

3.2.2 The Nord-Trøndelag Health Study 2006–2008 (HUNT3)

From October 2006 to June 2008, all individuals aged 20 or older in the county of Nord-Trøndelag were invited to take part in a health survey (HUNT3). Nearly 95,000 participants were invited, and 52% decided to partake in the study. Information on personality, life style factors, and work factors were collected by interview and two questionnaires. The first questionnaire was sent with the invitation to participate and was returned at the time of the interview. The second questionnaire was distributed at the interview and was completed at home and returned by mail. Of all participants, roughly 80% returned the take-home questionnaire. A study of non-participants in HUNT3 suggests that individuals who had a lower social position, poorer health, and who received disability pension were less likely to participate in the study (Langhammer, Krokstad, Romundstad, Heggland, & Holmen, 2012).

3.3 Study samples

3.3.1 Paper I

This paper was restricted to male residents for whom aerobic fitness information was available from the conscription examinations. In addition, at the start of follow-up (January 1, 2000) participants had to reside in Norway, be registered as employed, and not currently be on sick leave. The sample consisted of 227,201 men, or 70% of all men in the birth cohort. The mean age at start of follow-up was 29 years.

3.3.2 Paper II

This paper was restricted to individuals from the birth cohort who also participated in the HUNT3 study. Demographic data obtained from FD-Trygd indicated that as of 2006, 15,053 (2.3%) individuals from the birth cohort that had not died or emigrated, were residing in Nord-Trøndelag and were thus eligible to be recruited to the HUNT3 study; of these, 6,913 (46%) individuals were linked to participants in the HUNT3 study. We further restricted participation to only include individuals who were employed at the time of the interview (excluding self-employed individuals), and who had valid responses in HUNT3 on occupation, physical workload (assessed both at the interview and in the take-home questionnaire), and neuroticism. In total, 5,416 individuals, 3,222 women and 2,194 men, reported being employed. Due to long lines at the interview site, 631 participants (12%) were randomly selected to receive a short version of the interview that did not include an item on physical workload; therefore, these individuals were also excluded. Of those 3,328 individuals completing the full interview, 2,099 women and 1,229 men had completed the physical

workload questions and the neuroticism scale in the take-home questionnaire and had an identifiable occupational group. This comprised our final study population. The mean age in this sample was 36 for both women and men.

3.3.3 Paper III

The sample consisted of all individuals who, at age 18, had parents that were considered at risk of sick leave and who themselves were at risk during the year of their 33rd birthday. The sample was restricted to individuals born between 1974 and 1976, since reliable parental sick leave data was only available from FD-Trygd for this sub-cohort. This resulted in a total sample of 78,878 individuals (40,335 males and 38,543 females). By design, the age at follow-up of all study participants was 33 years.

3.3.4 Paper IV

The sample consisted of sibship pairs meeting the following criteria: both had to be employed for at least four months between 1992 and the end of 2003; neither could have died, emigrated or been granted disability pension prior to the beginning of follow-up; and the size of the sibship had to be two. In total, our study included 19,634 sibships. The youngest siblings, a total of 9,329 females and 10,305 males, comprised our study sample. The mean age was 21 for women, and 22 for men (range for both sexes, 15–35).

3.4 Measures

3.4.1 Sick leave data

In Paper III, one-year sick leave risk was the main research outcome, while in Paper I, II and IV time-to-sick leave was the main study outcome. In Norway, sick leave benefits are provided for members of the National Insurance Scheme that are unable to work due to illness, disease or injury. It covers all individuals who have worked for at least four consecutive weeks and earned at least half the public pension base rate unit in the preceding 12 months. The public pension base rate unit is adjusted annually and amounted to roughly 89,000 NOK in 2014. Most employees are entitled to three to eight days of self-certified sick leave (up to 12–24 days per year). For longer durations, however, a medical certification provided by a physician is required. The employer covers salary the first 16 days, while the National Insurance Scheme covers salary replacement for any sick leave days exceeding this period. The national database FD-Trygd, which goes back to January 1, 1992, contains the start and end-date for each sick leave episode exceeding 16 days (Akselsen et al., 2007). Ascertainment of consecutive sick leave episodes exceeding 16 days in the FD-Trygd

database is considered complete. We obtained sick leave data from January 1, 1992 through December 31, 2009. We defined sick leave as more than 16 days of consecutive sick leave. In Paper I, we also considered sick leave episodes lasting more than six consecutive weeks.

3.4.2 Sick leave diagnostic categories

In Paper I, II and III we considered diagnosis-specific sick leave episodes. For each sick leave episode registered in FD-Trygd, diagnosis has been provided by the patient's physician, who is required to label all sick leave forms with an International Classification of Primary Care (ICPC) diagnostic code (World Organization of National Colleges, Academies and Academic Associates of General Practitioners/Family Physicians, 1998).

In Paper I, we only considered sick leave episodes due to musculoskeletal diagnoses. We further considered musculoskeletal injuries and non-injuries (restricted to diagnoses of the upper extremity, neck and back).

For Paper II, we restricted the analyses to sick leave episodes that were not due to pregnancy-related diagnoses.

For Paper III, we performed several analyses according to the following diagnoses: all-cause, musculoskeletal, psychiatric, pregnancy-related, all but pregnancy-related, missing, back disorders, and depression. In Paper III, sick leave diagnoses were also relevant for the exposure variables (parental sick leave). The ICPC classification system was introduced in the early 1990s but was only partly in use in 1992. Prior to 1992, the Labour and Welfare Administration used a diagnostic classification system based on a 61-item code. This alternative coding system was used when the parental sick leave ICPC-code was missing.

3.4.3 Indicators of adult social position

Education (Paper I and IV)

Educational level, based on the first digit of the six-digit code according to the Norwegian Standard Classification of Education (Statistics Norway, 2003), was obtained from the National Education Database. The nine-level educational level code was collapsed into five levels: long tertiary (levels 7–8), short tertiary (level 6), upper secondary, complete (levels 4–5), upper secondary, basic (level 3), and lower secondary or less (levels 0–2). In Paper I, education was obtained for the highest completed education as of 1999 (ages 23–32 years). In Paper IV, education was obtained for the year in which follow-up started, ranging from 1992 through 2003 (ages 15–37 years).

Combination of Occupation and Education (Paper II)

In Paper II, adult social position was based on a combination of educational level and occupation, grouped into three categories. Occupation was obtained from an interview and coded by Statistics Norway according to the 1998 version of the Norwegian Standard Classification of Occupations (*Standard Classification of Occupations*, 1998), based on The International Standard Classification of Occupations (ISCO-88), which identifies ten main occupational groups (0–9). A large proportion of females clustered in few occupational groups. Additionally, the distribution of physical workload and sick leave according to education and occupation differed for men and women; we therefore opted to group social position slightly differently for women and men. For women, the highest social position (I) included executive managers and military personnel⁶ (groups 0–1) and participants with long tertiary education. The middle group (II) included professionals (group 2), associate professionals (group 3), clerks and service workers (groups 4–5), and participants with a short tertiary education. The lowest social group (III) included manual workers (groups 6–9) having upper secondary complete education or less. For men, however, associate professionals (group 2) were included in the highest social group (I) as opposed to the middle (II), while manual workers (groups 6–9) with upper secondary complete education were placed in the middle group (II) and not the lowest (I).

Industrial sector (Paper I)

In this paper, male participants were grouped into blue-collar and white-collar workers. We obtained the Standard Industrial Code (SIC94) (*Standard Industrial Classification*, 1994), based upon the European NACE classification, from FD-Trygd. Individuals with a SIC94 sector code from A to I were categorized as blue-collar workers, and individuals with code J to Q were placed into the white-collar industrial group.

⁶ Military professionals were placed into this category because they primarily have leadership positions.

3.4.4 Indicators of social position in childhood and adolescence

Parental education level

We determined the educational level of each parent (as measured when the participant was 16 years old) and classified the variable according to the five educational levels described previously. In Papers I, II and IV, we combined maternal and paternal education into one variable, while in Paper III, maternal and paternal education were included as separate categories. In Paper II, the two highest levels were collapsed (short and long tertiary), resulting in four levels.

Parental income (Papers II and III)

Parental income was obtained in FD-Trygd, which provides annual pensionable income, reported in public pension base-rate units, adjusted each year. In Paper II, family income during childhood and adolescence was calculated by averaging the mean of the sum of both parents' income during a 19-year period (when the participant was aged 0 through 18 years). If the father's identity was unknown, only the mother's income was used in this calculation. In Paper III, we used paternal income in the calendar year when the index person turned 18. In both Paper II and III, the income variable was included in the model as quartiles.

Parental disability pension (Papers II and IV)

Data on whether parents received disability benefits before study participants had turned 18 was obtained from the Norwegian Labour and Welfare Administration.

3.4.5 Aerobic fitness (Paper I)

Aerobic fitness tests were carried out as a part of military service conscription in the Norwegian Armed Forces. At the time of examination, 98.3% of the participants were 18 or 19 years old. Until 1989, the aerobic fitness test was based on an ergometer-cycling test, but in 1989–1990 was replaced by a treadmill test. Both tests indirectly estimated aerobic capacity by measuring heart rate (cycling) or blood lactate levels (treadmill) after a fixed exercise session. The conscript test personnel classified aerobic fitness as high, medium or poor based on the test results. In the treadmill test, the cut-off points for high and poor fitness were lactate levels of 3 and 9 mmol/L, respectively.

3.4.6 Physical workload (Paper II)

Physical workload measures were obtained in HUNT3 during the interview and in the take-home questionnaire using the following three questions: (i) "Are you exposed to heavy lifting?"; (ii) "Is your work so physically demanding that you are often worn out after a day's

work?"; and (iii) "If you have had paid or unpaid employment, how would you describe your job?" Question (i) was rated on a 3-point scale from 0 (no) to 2 (often); question (ii) on a 4-point scale from 0 (yes, almost always) to 3 (never, or almost never); and question (iii) on a 4-point scale: 0 (work that mostly involves sitting), 1 (work that requires much walking), 2 (work that requires much walking and lifting), and 3 (heavy physical work). To account for question (i) being on a scale 1-point less than the other two questions, non-zero responses were weighted by one extra point, resulting in a 3-point scale with values 0, 2, and 3. The scores were then summed to create a physical workload index (and the sum score incremented by one, resulting in a 1–10 point index), with higher values indicating greater physical workload. There was a linear relation between adult social position and physical workload, and the variable appeared to be approximately normally distributed. A dichotomous physical workload variable was also created for descriptive purposes, where a sum score below the median represented low physical workload.

3.4.7 Personality trait, neuroticism (Paper II)

Neuroticism was assessed with a modified version of the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975), which was administered as a take-home questionnaire in HUNT3. Participants responded to six questions that had been selected for inclusion in the short-form, based on showing highest predictive value with the full-scale questionnaire (Tambs, 2004). The same study showed high correlations between scores from the original instrument and the short-form instrument ($r=0.90$). The six questions were rated on a 2-point scale, either zero (*no*) or one (*yes*). A neuroticism index was computed by summing answers to the six questions. Higher values on this index indicate that participants had higher levels of neuroticism. A dichotomous neuroticism variable was created based on the index, for descriptive purposes, with low neuroticism representing a score below the median.

3.4.8 Other military conscription data (Paper I)

In Paper I, we used data on intellectual ability, body mass index (BMI), and musculoskeletal condition. The intellectual ability test was recorded as stanine scores, that is, a nine-point scale from 1 to 9 with a mean of 5 and standard deviation of 2 (Sundet, Barlaug, & Torjussen, 2004). The stanine scores have been found to have a correlation of 0.73 with the Wechsler Adult Intelligence Scale (Sundet, Tambs, Magnus, & Berg, 1988). Body weight and height were measured and BMI categorized as underweight ($<18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25\text{--}29.9 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$). A conscript physician assessed the physical functioning of hands, arms, back, and gait. We merged these four items

to create a musculoskeletal-condition variable with five ordered categories from “not affected” to “seriously affected”.

3.4.9 Aggregate level variables (Paper I)

In Paper I, we used a sick leave variable indicating the overall sick leave proportion in a given enterprise. We first identified the number of men (born 1967–1976) employed in a given enterprise in the year 2000. The individual enterprise was identified by the organization number in FD-Trygd. We then computed the fraction of men in a given enterprise who had experienced a sick leave episode, by dividing number of men with a sick leave episode in 2000 in a given enterprise, by the total number of men in that enterprise in 2000 (after first subtracting both numerator and denominator by one).

3.5 Study design

The studies in all the four papers used observational study design. Specifically, we used a prospective cohort design. The specific follow-up periods differed in the respective studies; an overview of the timing of the assessment of early lifecourse covariates, exposures, and outcomes is shown in Figures 5—8 (Papers I—IV, respectively).

Paper I

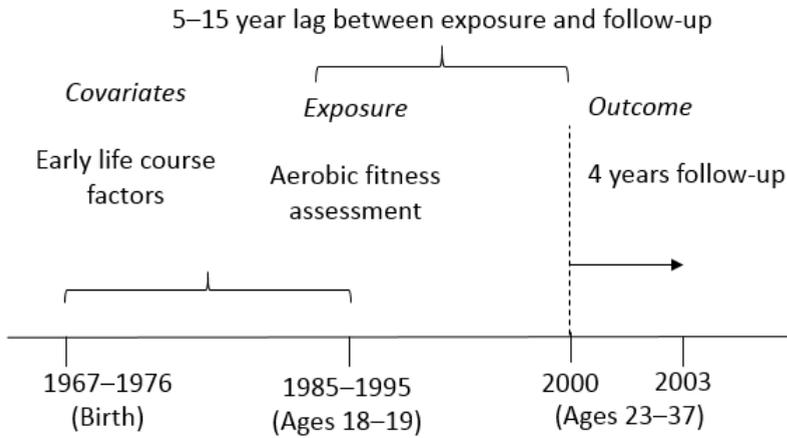


Figure 5. Study design and follow-up, Paper I

Paper II

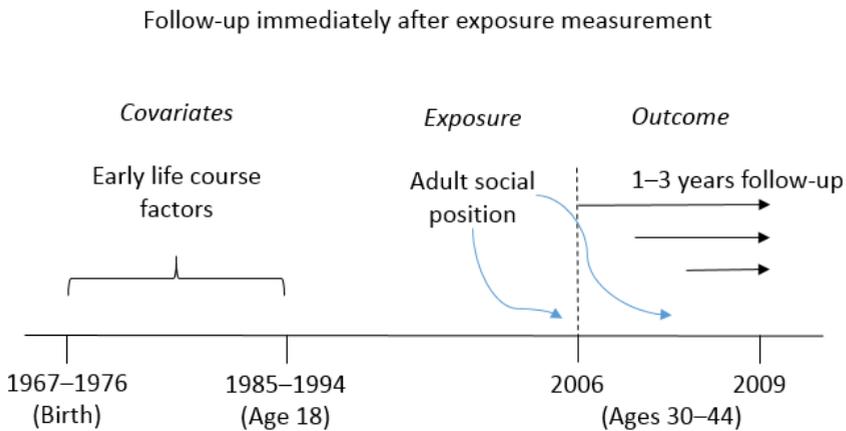


Figure 6. Study design and follow-up, Paper I

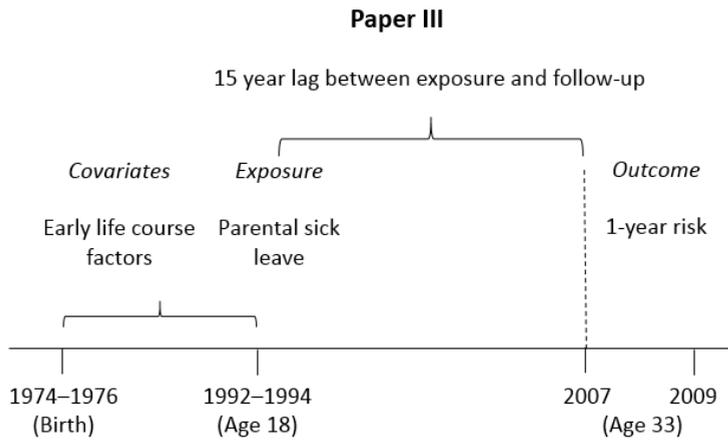


Figure 7. Study design and follow-up, Paper III

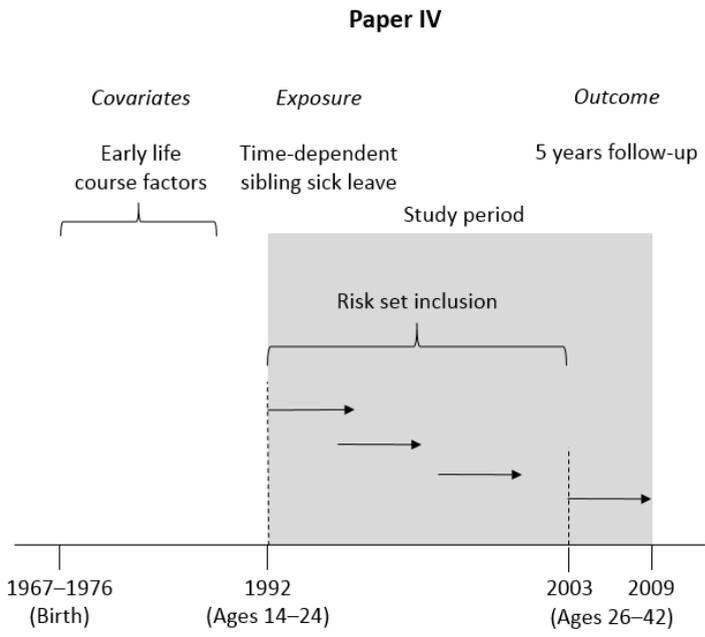


Figure 8. Study design and follow-up, Paper IV

3.6 Model selection/analytic choices

3.6.1 Mediation.

Papers I and II use mediation analyses in order to understand the mechanisms that link the exposures to sick leave. The general approach to mediation in the social sciences has been hugely influenced by the paper by Baron and Kenny (1986), which has been cited more than 50,000 times on Google Scholar. This work also appears to have influenced the typical epidemiological approaches to mediation (Kaufman, 2010). Whilst the topic of mediation analysis techniques have been written about extensively in the social sciences, and there exist at least three books on the topic (Hayes, 2013; Jose, 2013; MacKinnon, 2008), it has not, until recently (VanderWeele, 2015), been given serious treatment in the epidemiology textbooks. The field has developed considerably over the past decade or two, and it is now widely recognized that the methods that sprung out of the Baron-Kenny approach to mediation only works in the special case of linear models without interactions (Cole, 2002; Kaufman, Macle hose, & Kaufman, 2004; VanderWeele & Vansteelandt, 2009). Further, several authors have recognized that the Baron-Kenny approach does not enabled a general causal definition of mediation (MacKinnon, 2008). Building on the counterfactual framework by Pearl (Pearl, 2009), a formal approach to mediation analysis has now been developed. Robins and Greenland (1992), and Pearl (2001) showed that a total effect can be broken down into natural direct and indirect effects, regardless of the underlying statistical model.

In Paper I, we use a traditional Baron-Kenny approach, while in Paper II, we use causal mediation model in a survival setting. I will first discuss the Baron-Kenny approach, including its limitations, followed by a brief introduction to the counterfactual-based decomposition of total effects into natural direct and indirect effects. Last, I will present the causal mediation analysis method developed by Lange and Hansen (2011) which enables the decomposition of total effects into natural direct and natural indirect effects using survival data, and which was used in Paper II.

Classic regression approach to mediation analysis

While the approach is often simply referred to as the Baron-Kenny approach, it should be noted that others had proposed it previously (Judd & Kenny, 1981; Sobel, 1982). The causal diagram below shows how they conceptualize a mediator variable (Baron & Kenny, 1986). The path diagram in Figure 9 shows the causal relation between an independent, or exposure variable (X), the outcome (Y), and the mediating variable (M).

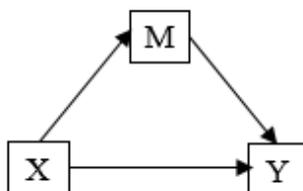


Figure 9. Baron and Kenny's causal model for depicting mediation

They lay out a causal-steps procedure to enable the identification of mediation, and they present two procedures for the parametric estimation of mediation: the product method and the difference method. Both the causal-steps procedure and the estimation methods are based on estimating the following three linear regression models:

- | | | |
|----|---|---------|
| 1) | $Y = \theta_0 + \theta_1 X + \epsilon_y$ | Model 1 |
| 2) | $M = \alpha_0 + \alpha_1 X + \epsilon_M$ | Model 2 |
| 3) | $Y = Z_0 + \theta_2 X + \beta_2 M + \epsilon_y$ | Model 3 |

According to their causal-steps procedure, in order for a variable to be defined as a mediator, the following four criteria have to be met: (i) changes in X have to be associated with changes in M (path X to M), (ii) there is a significant association between the mediator and the outcome (path M to Y), (iii) changes in the exposure significantly affect the outcome (total effect of X on Y), and (iv) when the mediator is controlled for, a previously significant relation between the exposure and outcome is no longer significant, with the strongest demonstration of mediation occurring when the path from the independent variable to the outcome variable is zero.

To obtain a measure of the strength of the indirect effect, Baron and Kenny (1986) proposed two approaches. In the product method, one multiplies the coefficients $\alpha_1\beta_2$ (obtained from models 2 and 3, respectively) (Alwin & Hauser, 1975; Judd & Kenny, 1981; Sobel, 1982). In this approach, they conceive of the total effect of the exposure as θ_1 (model 1) and the direct effect as θ_2 (model 3). In the difference method approach, one subtracts the coefficient θ_2 (model 3) from θ_1 (model 1) (Judd & Kenny, 1981).

Extensions of Baron-Kenny approach in epidemiology

In epidemiology, the most common way of doing a mediation analysis (Kaufman et al., 2004; Kaufman, 2010; Richiardi, Bellocco, & Zugna, 2013) is inspired by the difference method

(Kaufman, 2010). Usually, the approach is to estimate an exposure effect adjusting for confounders, and compare this with the same parameter estimated in a second model that also controls for the mediator. The difference between these two estimates, expressed as a proportion of the first estimate, is generally interpreted as the effect of the exposure that is mediated by the additional variable (Kaufman, 2008, 2010). This number is often further interpreted as the percent of the outcome that could be removed if the path through the mediator was blocked (Kaufman, 2010).

Critique and limitations of the Baron-Kenny approach

In recent years, the limitations of the Baron-Kenny approach have received considerable attention. The first issue is the requirements of the four causal steps in order to identify mediation. While requirements (i) and (ii) have been accepted, requirement (iii) has been critiqued by many scholars (MacKinnon, 2008). The reason is that the effect of X and Y does not need to be statistically significant for M to be a mediator; direct and mediated effects may have opposite signs, and could cancel one another out (often called inconsistent mediation). In addition, requirement (iv) is also not necessary because mediation can be partial or complete

Further, there has been an increased focus on when it is appropriate to use the Baron-Kenny method, and when it is not. The original development of the mediation analysis was formulated for multiple regression models, in which additive effect measures and linear contrast measures were obtained. This implies that the methods developed in this framework are not generalizable to nonlinear models, for discrete mediators and outcomes, as well as non- or semi-parametric models (Imai, Keele, & Tingley, 2010). The assumptions imposed in the original development of the decomposition methodology involved additivity of effects and linear contrast measures, neither of which are typical of the analysis of discrete events, such as occurrence of a diseases (Kaufman et al., 2004); the application of the difference method approach in epidemiology is therefore rarely defensible and prone to substantially misleading inference (Kaufman, 2010).

Another issue that has received considerable attention is that interpretation of direct and indirect effects are quite vague in the Baron-Kenny approach. The direct effect has been defined as the effect that is not mediated by other variables in the model, or the change in Y while the mediator is held *fixed*. The total effect is estimated by the effect of changing the exposure variable. However, the definition of indirect effects has remained incomplete, and, save for asserting inequality between direct and total effects, the concept of “indirect effect was deemed void of operational meaning” (Pearl, 2001).

Causal mediation analysis

A new approach to mediation analysis that has sprung out of the work of Pearl (2001) and Robins and Greenland (1992), has given new definitions to direct and indirect paths. In this new conceptualization, definitions of direct and indirect effects are given that do not involve fixing variables in the model. Further, the definitions of direct and indirect effects do not require a commitment to functional or distributional forms and are therefore applicable to models with non-linear interactions and both continuous and categorical variables. The framework is rooted in counterfactual causality. An in-depth discussion of causality is beyond the scope of this thesis. Detailed accounts of counterfactual theory for the social sciences (Morgan & Winship, 2007) and epidemiologists (Hernán & Robins, 2016) give accessible introductions on the topic. I will here give a brief explanation.

Counterfactual causality framework

The intuitive way of thinking about counterfactual causality is to compare the outcome if a person had been given some treatment, compared to if he or she had not. The difference between these two outcomes is what would be considered the individual causal effect. To put this in more formal notation, one can define the counterfactual outcome $Y(X)$, which denotes the counterfactual outcome that we would have observed for that individual had an exposure X been set from x^* to the value x through some intervention or manipulation (Hernán, Hernández-Díaz, & Robins, 2004). In the case where the exposure is dichotomous (1 representing treated, 0 representing untreated), the individual will have two counterfactual outcomes $Y(1)$ and $Y(0)$. If these two counterfactual outcomes are different, then we would say that the treatment had an *individual causal effect* of treatment. But we can in general only ever observe one of these counterfactual outcomes. However, we can sometimes observe *average causal effects*, which are defined as the expected difference between both counterfactual outcomes for the same study population: $P(Y_x = y) - P(Y_{x^*} = y)$. For an introduction into when these we can infer average causal effects, the reader is referred to the book by Hernán and Robins (Hernán & Robins, 2016).

Total, natural and controlled effects.

To illustrate the different conceptualization between natural and controlled effects, I consider an example based loosely on examples given by Pearl (2001). Low social position increases the risk of sick leave, in part due to the more hazardous working conditions experienced by this group. If one were interested in determining how detrimental to health low social position was for the population as a whole, one would want to estimate the total effect of the low

social position on sick leave. In a mediation setting, the counterfactual notation is extended to include counterfactual outcomes that include the level of the mediator. Let $Y(X, M)$, denote the counterfactual sick leave status under exposure $X=x$ (1: low social position; 0: high social position) and working conditions as $M=m$ (1: hazardous working conditions; 0: non-hazardous working conditions). We can conceptualize direct effects and indirect effects in two different ways: controlled and natural.

Controlled direct effects

The controlled direct effect is the effect of the exposure on outcome that would be observed if the mediator was controlled uniformly at a fixed value. We thus need to estimate a controlled effect for each level of the mediator.

What would the controlled direct effect of social position be if everyone had *non-hazardous* working conditions ($M=0$)? The difference in sick leave risk that we would observe if we could change social position from high to low if everyone had non-hazardous working conditions would be:

$$E\{Y(1,0) - Y(0,0)\}$$

What would the controlled direct effect of social position be if everyone had *hazardous* working conditions ($M=1$)? The difference in sick leave risk that we would observe we could change social position to low if everyone had hazardous working conditions is given by:

$$E\{Y(1,1) - Y(0,1)\}$$

In linear systems, direct effects are fully specified by the corresponding path coefficients, and are independent of the values at which we hold the mediator. In nonlinear systems, however, those values would in general modify the effect of X on Y (Pearl, 2001).

Natural direct effects

In this setting, it is not realistic to think of forcing the mediator to be the same for all subjects. Rather, this approach allows for natural variation in the level of the mediator between subjects. A subject's natural level of the mediator is taken to be the counterfactual value $M(0)$ it would have taken if the subject were unexposed. This approach requires knowledge of individual's natural behavior. The natural direct effect is defined as the difference in sick leave risk that we would observe if we could change from high social position to low social

position and working conditions remained the same as though they were still in the high social position group:

$$E\{Y(1, M(0)) - Y(0, M(0))\}$$

Robins and Greenland (Robins & Greenland, 1992) define the natural indirect effect as the total effect minus the natural direct effect:

$$\begin{aligned} & \text{total effect} - \text{natural direct effect} \\ &= E\{Y(1, M(1)) - Y(0, M(0))\} - E\{Y(1, M(0)) - Y(0, M(0))\} \\ &= E\{Y(1, M(1)) - Y(1, M(0))\} \end{aligned}$$

If the assumptions of no confounding are met, the average controlled direct effect, natural direct effect, and natural indirect effect, conditional on the covariates, are identified by the data (Pearl, 2001).

Analytic approaches to causal mediation analysis

In the past decade, there has been an explosion in causal methodologies that are suitable for mediation analysis. The newly published book by VanderWeele (2015) provide a very comprehensive overview of the methods that have been developed, and which analytic approach is suitable in a given scenario. In some cases, the “old” methods give the same result as the new. In the case of an outcome that is either binary or normal, a number of techniques have been developed to assess the relative importance of the various paths from exposure to the outcome (Hafeman & Schwartz, 2009; Petersen, Sinisi, & van der Laan, 2006; Rubin, 2004; VanderWeele, 2009). However, until recently, there was no such approach in survival analysis (Lange & Hansen, 2011).

3.6.2 Causal mediation analysis in survival setting

Lange and Hansen formulated a counterfactual approach for mediation analysis in the survival framework (2011). The method allows for the estimation of the total effect of changing an exposure on a survival outcome, measured as the number of additional events per unit of time. Furthermore, the method can decompose this number of additional events into a natural direct pathway and a natural indirect pathway through the mediator.

The mediation framework relies on the definition of two models. First, he defines an Aalen additive hazards model (Aalen, Borgan, & Gjessing, 2008b). This model is used

instead of the proportional Cox model because the assumption of proportional hazards can never be met both in a model with, and without, the mediators. This model yields an estimate of the absolute change in the rate when comparing a given exposure group to a reference group. This estimate can be interpreted as the “rate difference (number of additional spells of sick leave in the group per person-time unit at risk), compared to the reference group” (Lange & Hansen, 2011). Second, they lay out a mediator model, where the mediator is a normal variable that can be modeled by a linear regression. To model the causal effect of the exposure on the outcome, they define a set of counterfactual variables, in line with what was shown in the previous section, except here the outcome is time-to-event. For a specification of counterfactual variables and definitions, refer to the paper by Lange and Hansen (2011). The method allows one to estimate the total effect of a hypothetical change in adult social position, measured by the change in hazard rate for time-to-first-sick-leave-spell.

3.6.3 Social interaction (Papers III and IV)

In Papers III and IV, our goal was to estimate family association in sick leave behavior, and try to shed light on whether social interaction was compatible with the findings. In Paper III, the aim was to assess whether exposure in adolescence was associated with sick leave later in life – this design therefore had a relatively long latency period between the exposure and the outcome. Also, data on parental sick leave was rather limited, in that we did not have event-histories for parental sick leave. Further, we wanted to look at sex differences in sick leave, which implied that an additive rather than relative approach was called for. For Paper IV, we had a very different situation, in which we were more interested in the possible immediate effect of sibling exposure on sick leave. That is, we wanted to see if we could disentangle the relation in some time-dependent fashion. For this aim we chose a dynamic Cox regression. A description of data, goals of analysis, and an explanation of what a dynamic Cox model is, is presented below.

Description of data structure and analytic challenges in Paper IV

Figure 10 shows the hypothetical follow-up data for an older and younger sibling over time in Paper IV. During follow-up, the older sibling has three sick leave episodes (dashed lines), while the younger sibling has three sick leave episodes (solid lines) and is absent from work for one period due to maternity leave (dotted line).

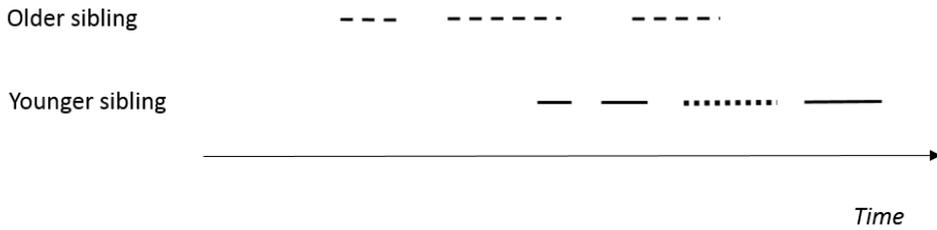


Figure 10. Example of a follow-up pattern for younger and older sibling in Paper VI, showing older sibling’s sick leave episodes (dashed line), younger sibling’s sick leave episodes (solid line), and a period of maternity leave (dotted line).

The aim was to assess whether exposure to an older sibling’s sick leave episode would increase propensity for a new sick leave episode. This analysis poses several challenges. First, the direction of sibling influence may be reciprocal, so that not only may the older sibling influence the younger sibling, but the younger sibling may in turn influence the older sibling. Second, siblings are similar to one another in ways that may lead them to have corresponding propensities to sick leave. This includes not only having a shared genetic endowment, but also attaining similar levels of education and sharing family conditions during childhood and adolescence. Third, having had a sick leave episode, or the underlying illness that lead to the sick leave episode, may increase the rate of having future sick leave episodes. Fourth, age—and age-dependent factors (such as having children and getting divorced—may increase the sick leave rate. Older siblings therefore likely start off with a higher propensity to sick leave. As time passes, younger siblings naturally develop an age-dependent increase in sick leave propensity, which could potentially confound the estimates. Fifth, siblings may jointly experience conditions such as national trends in sick leave tendencies that cause their sick leave rates to vary at the same time. Last, participants are not always at risk during the observation period for a new sick leave episode. This includes the time they are currently having a sick leave episode, and during maternity leave.

What type of analysis would be appropriate to tackle these problems? In order to deal with the reciprocal issue, and time-dependent issues of confounding variables, it seems apparent that the best approach to analyzing this is to use a method that allows for an instantaneous analysis of risk. That is, rather than starting with a “baseline” exposure value measured at whatever time one decide to start follow-up, one would update the covariate value in time as it is changing. Second, in order to model the changing risk of exposure, or possibly individual frailty, it would be ideal to be able to use a model that allows for the

incorporation of frailty and modeling how the past influences the future. Third, a more technical issue is that sick leave is strongly skewed, with the large majority having very few sick leave episodes, and a minority of individuals having many sick leave episodes (Hensing, 2004). Last, we need a method that allows for discontinuous periods of risk (e.g., during maternity leave), as it is recognized as very important to properly define time at risk (Hensing, 2004). Considering these analytic aims and constraints in the structure of the data, which options do I have then?

Non-recurrent event approaches

While the basic structure of the data is recurrent event data, the most simplistic would be to ignore all events except the first one, and treat the analysis as a non-recurrent event analysis. Data could then, for instance, be analyzed using logistic regression or a univariate Cox model (Gill, Zou, Jones, & Speechley, 2009; Twisk, Smidt, & de Vente, 2005). Given that the goal of the analysis was to incorporate time-dependent exposures, this rules out the logistic regression approach. I could have fit a univariate Cox model, using time-dependent covariates to incorporate the sibling sick leave exposure; however, it has been shown that recurrent event methods are more efficient (Gill et al., 2009) and reveal a different picture of the effect of the exposure on the outcome (Gill et al., 2009; Twisk et al., 2005). Further, by using a univariate Cox approach, I would not be able to include the past history of sick leave into the model (which will be discussed later). The non-recurrent approaches thus seem rather unfitting.

Recurrent event approaches

Quite a few authors have written applied introductions to ways of analyzing recurrent events (Amorim & Cai, 2015; Gill et al., 2009; Guo, Gill, & Allore, 2008; Kelly & Lim, 2000; Twisk et al., 2005). The easiest way would be to treat data as count data (Amorim & Cai, 2015; Gill et al., 2009; Twisk et al., 2005), which would imply the use of methods based on, for instance, logistic regression approaches for recurrent event data (e.g., GEE analysis or random coefficient analysis) or Poisson regression (Christensen, Andersen, Smith-Hansen, Nielsen, & Kristensen, 2007; Gill et al., 2009; Navarro, Reis, & Martín, 2009). Several limitations to the Poisson model are apparent. First, a Poisson approach does not enable the inclusion of time-dependent exposures. Second, the Poisson model does not take into account that people's sick leave hazard could change over time, rather the sick leave hazard is assumed to remain constant over the follow-up period. Again, this rules out the goal of the current analysis. Further, it is only a reasonable analytic approach if everyone is followed for the same amount of time, which is unrealistic for sick leave data (Christensen, Andersen, et al., 2007). Survival

analysis is therefore preferred when follow-up time varies among participants, or when there are time-dependent covariates or time-dependent effects.

Survival recurrent event models

Several modeling choices have been proposed to handle recurrent event survival data, mostly in the biostatistics literature (Hougaard, 2000; Kalbfleisch & Prentice, 2002; Therneau & Grambsch, 2000). For the more applied reader, introductions and comparisons between the models are also available (Amorim & Cai, 2015; Gill et al., 2009; Twisk et al., 2005). The recurrent event approaches are based on extensions of the Cox model, and the ones most commonly discussed approaches in the applied papers are the models referred to as Anderson Gill (1982), conditional (Prentice, Williams, & Peterson, 1981), and Wei, Lin, and Weissfeld model (1989). Other approaches include frailty models (Hougaard, 2000) and dynamic models (Aalen et al., 2008b; Aalen, Fosen, Weedon-Fekjær, Borgan, & Husebye, 2004).

One major distinction between the approaches mentioned above is how future events are related to past events. Marginal models—Anderson Gill, conditional, and Wei, Lin, and Weissfeld—assume that future events depend only on the immediate past. The three models differ, though, in terms of how analysis time is defined, how one treats the baseline hazard, and how one deals with the dependency structure between the events. In the Anderson Gill models, one uses a total time scale, and a common baseline hazard for all events. One thus estimates an exposure effect irrespective of number of events. A requirement for this model is that the dependence structure between event times can be explained by time-dependent covariates. The conditional model⁷ is analyzed using a specific baseline risk for each stratum, based on the number of prior events during follow-up. This approach produces an event-specific effect for each covariate. In this model, the effect of the covariates may vary from event to event. Further, time can be incorporated either as total time or gap-time (time since previous event). This approach might be preferable if one thinks that the effect of an exposure changes according to how many sick leave episodes one has had. In the Wei, Lin, and Weissfeld model approach, one treats the analysis essentially as a competing risk problem, using total time scale for each of the events. For each event, there will be a separate stratum, allowing a separate underlying baseline hazard for each strata. This approach is more relaxed

⁷ It seems a bit counterintuitive that a model named “conditional” would be considered marginal. It is conditional in respect to time at risk for a new sick leave episode (which is conditional on a prior event having occurred), but marginal in the sense that one estimates an overall effect parameter based on a fit that “ignored correlation followed by a corrected variance” (Therneau & Grambsch, 2000).

than the Anderson Gill method, and does not require time-varying covariates to reflect the past history of the process (Aalen et al., 2008b).

Seen as a whole, in the marginal approach, one does not try to model the development over time. In contrast to that, frailty models and dynamic models assume dependency between events and try to model it. That is, one views the dependencies between events as resulting from some underlying susceptibility to having the event. In the frailty model approach (Aalen et al., 2008b; Hougaard, 1995, 2000; Therneau & Grambsch, 2000), these dependencies are modeled as shared random effects arising from some distribution. Frailty models make very specific assumptions about effect of time, assuming fixed frailty for each individual, though this may not be a reasonable assumption. Christensen et al. discuss this issue in relation to sick leave data, suggesting that the frailty of an individual is probably more likely to change over time according to the underlying illness process (Christensen, Andersen, et al., 2007). An alternative approach to the frailty modeling is the dynamic model, which will be briefly discussed in the next section.

Dynamic recurrent event model

While the frailty models viewed frailty as something fixed, an alternative to this is to view individual frailty as a process that changes over time. One alternative is to model this dependence using internal time-dependent, or dynamic, covariate. Kalbfleisch and Prentice (2002) distinguished between an *internal* versus *external* time-dependent covariate. An external time-dependent covariate is not directly related to the event process. An example of this might be the age of an individual. An internal time-dependent covariate, on the other hand, arises from the individual under study. Examples might include marital status, number of children, and lifestyle factors. A dynamic covariate is a special case of an internal time-dependent covariate, where the covariate is directly linked to processes of the outcome under study. An example might be if one were studying sick leave, and sick leave itself is included in the model. These covariates sum up important aspects of development under study that may contain prognostic information. Dynamic covariates are given a more comprehensive treatment in Aalen et al. (2008a).

3.7 Statistical analysis

All analyses were done using the statistical software Stata (StataCorp, College Station, TX, USA) and the open-source software R (R Development Core Team, 2014).

An overview of the aims and analytic approach is provided in Table 1.

Table 1. Summary of the aims and methods of Papers I–IV

	Paper I	Paper II	Paper III	Paper IV
Study aim	Estimate associations between aerobic fitness at age 18–19 and sick leave 5–15 years later	Estimate degree of adult social position attributable to direct versus indirect effects through physical workload, taking into account early lifecourse factors	Estimate intergenerational association in sick leave risk, and whether there is a stronger generational effect for women	Estimate if exposure to sibling sick leave is followed by increased sick leave hazard, while taking into account individual propensity to sick leave
Exposure	Aerobic fitness at age 18–19	Adult social position	Parental sick leave at age 18	Sibling sick leave (time-dependent)
Sick leave outcome	Time-to-sick-leave-episode	Time-to-sick-leave-episode	One-year risk of any spell (0/1)	Time-to-recurrent-sick-leave-episode
<i>Diagnoses considered</i>	Musculoskeletal (injury and non-injury)	All-cause (not pregnancy-related)	<ul style="list-style-type: none"> •All-cause •Musculoskeletal •Psychiatric •Pregnancy-related •All-cause (no W) 	All-cause
Follow-up	4 years	2–4 years	1 year	5 years
<i>Time at risk</i>	2000–2003	2006/2008–2009	2007–2009	1992–2008
<i>Study period</i>				
Analysis	Cox survival analysis, traditional mediation analysis	Causal mediation analysis, using Aalen’s additive hazards survival model	Binomial linear regression	Cox survival analysis for recurrent events, using time-dependent exposure and an internal time-dependent covariate

3.7.1 Generalized linear models

In Papers I and III, we fit generalized linear models. In Paper I, we fit a Poisson regression model in order to compute the adjusted population attributable fraction, which will be discussed in more detail below.

In Paper III, we fit an additive binomial regression model to estimate the one-year risk difference using Stata's `binreg` command. We estimated whether the additive 1-year-risk difference in those exposed to parental sick leave 15 years earlier was higher than those not exposed.

3.7.2 Population attributable fraction

The population attributable fraction (PAF) is the proportional reduction in population sick leave that would occur if exposure to a risk factor were reduced to the reference exposure category. In a causal sense, PAF is the proportional reduction of the outcome that would occur in a population if exposure to the risk factor were eliminated.

PAF (λ) is a function of the population probability of an outcome, $P(D)$, and the probability of outcome among the unexposed (Eide & Heuch, 2001), $P(D|\bar{E})$.

$$\lambda = \frac{P(D) - P(D|\bar{E})}{P(D)}$$

3.7.3 Cox Regression

A univariate Cox regression model was fit in Paper I. We estimated whether the hazard of a first musculoskeletal sick leave episode was higher among those with poor and middle aerobic fitness, compared to those with high aerobic fitness. We also performed separate analyses in which we only considered the sub-categories non-injury and injury musculoskeletal sick leave. Participants were followed from January 1, 2000 to the end of 2003 (or until an event or censoring). Study participants were censored if they died, emigrated or went on disability pension, or had a non-musculoskeletal sick leave episode. For further details on study-design, see Figure 5, Paper I. Assessment of interaction between the exposure and mediator was done by testing if the association between aerobic fitness and sick leave differed in strata of white and blue collar workers, as suggested by Altman and Bland (2003).

3.7.4 Traditional mediation analysis (Baron-Kenny) using Cox model

We performed a traditional mediation analysis (derived from the Baron-Kenny approach) in Paper I by comparing the association between aerobic fitness and sick leave in a model that adjusted for mediators, compared to one that did not (both models adjusting for the

confounders: year of birth, intellectual capacity, BMI, musculoskeletal function, and parental education level). We considered the mediating variables industry (white and blue collar), education, and an indicator of enterprise sick-leave-mean. The reduction in estimates in this latter model, compared to former, was considered to constitute the part of the aerobic fitness effect that was due to the mediator.

3.7.5 Causal mediation analysis using Aalen's additive hazards model

In Paper II, we apply a mediation analysis with a causal interpretation using a newly developed method by Lange and Hansen (Lange & Hansen, 2011). The theoretical underpinnings of this analysis are described in more detail in section 3.6.

The mediation analysis involved two steps. In the first step, we estimated the effect of adult social position (combination of education and occupational position) on physical workload (the mediator) in a linear regression model. Parameter estimates and standard errors from this model were used for the estimation of the indirect effect of adult social position on sick leave. We controlled for neuroticism, age, marital status, parental education, parental disability benefits, and parental income.

In the second step, we estimated the direct effect of adult social position and physical workload on sick leave in an additive hazards model. The total effect of adult social position on sick leave is given by the sum of the direct effect and the indirect effect. The direct effect of adult social position on sick leave is obtained directly from the additive hazard model. The indirect effect is given by the product of the parameter estimates for the regression of physical workload on adult social position (linear model) and the parameter estimate of physical workload on sick leave (additive hazards model). The mediated proportion is given by the quotient of the indirect divided by the total effect. For the direct effect, 95% confidence limits are available from the additive hazard model, whereas limits for the indirect and total effects as well as mediated proportion were computed from the standard errors and covariances in line with Lange and Hansen (2011). A copy of the syntax is provided in Appendix A.

3.7.6 Dynamic cox regression model (Paper IV)

In Paper IV, we wanted to estimate whether exposure to an older sibling's sick leave episode was followed in an increase in sick leave hazard. Since we wanted to incorporate an individual history into the model, we chose a dynamic recurrent event model (as described in more detail in section 3.6). The counting process formulation on which this model is based allows for discontinuous periods of risk (Therneau & Grambsch, 2000). The absence pattern

(pattern of not being risk) is described by the process $Y_i(t)$ which is zero when the sibling is not at risk for sick leave, and one otherwise.

Time-dependent exposure

The exposure, sibling sick leave, could occur multiple times over the 5-year follow-up period. To account for the change in exposure, sibling sick leave was incorporated into the model as a time-dependent covariate. This exposure was set to either zero or the total number of sibling sick leave episodes counted before enrolment, and was incremented by one for each episode observed thereafter. Since few siblings had a high number of sick leave episodes, exposure levels above three were collapsed, resulting in five exposure categories (0, 1, 2, 3 and ≥ 4). To account for the fact that a sibling sick leave episode could not influence the participant's propensity for sick leave until after the episode had occurred, the variable was lagged, such that the exposure changed value for the subsequent risk interval.

Dynamic covariate

A time-dependent covariate, counting the total number of past sick leave episodes, was meant to account for the participant's unmeasured propensity to sick leave. This variable is a type of internal time-dependent covariate in that it incorporates aspects of the outcome into the model. We constructed this variable in the same way as the exposure variable, setting it either to zero or the total number of sibling sick leave episodes counted before enrolment, and incrementing it by one for each episode observed thereafter. An alternative would have been to model the frailty using a frailty model, where the individual's frailty was described by a random gamma frailty variable.

Other time dependent covariates

We accounted for age-dependent factors by including age (3-month categories), marital status (updated daily), and number of births (available for women only; updated daily). To account for the nonlinear relationship between age and risk of sick leave, we applied the fractional polynomial method to identify a better functional fit for age (Royston & Altman, 1994). The best fitting model included the terms age^{-2} and age^{-1} for females, and $age^{-2} \times \ln(age^{-2})$ for males.

Time-invariant covariates

To control for time trends in sick leave rates, we created a variable representing year and quarter that follow-up period commenced. A participant's follow-up period could commence in one of four quarters between 1992 and 2003, resulting in 44 categories. To account for factors relating to shared background, we included parental education, parental disability, and mother's marital status, while educational similarities were accounted for by including the participants' and older siblings' educational level at enrolment. Results of non-proportionality tests (Andersen, Borgan, Gill, & Keiding, 1993; Therneau & Grambsch, 2000), estimated using Stata's `phtest estat` function (Cleves, Gould, Gutierrez, & Marchenko, 2008) showed a disagreement for the proportionality assumption for all shared background variables and education. We therefore included these confounders in the model as stratifying variables using the `stcox` option *strata*. In this context, stratifying means that the variables are added as control variables to the model, which circumvents the restriction of the proportional hazard assumption (Therneau & Grambsch, 2000).

Model fitting

All models were fit separately by sex. We accounted for the correlation of observations from the same person by using a robust variance estimator. Based on inspection of the cumulative hazard plots, it was apparent that the effect of exposure appeared to be dependent upon past sick leave history. We therefore split the analysis at the time of the first sick leave episode, and fit two separate models; in a univariate model, we estimated the rate of sick leave from study entry up to first sick leave, and in a multivariate model, for those experiencing more than one sick leave episode, time from the first sick leave episode to recurring sick leave episode(s).

Creation of the risk set

In order to fit the models, we created a dataset using the counting process style of input (Cuzick, 1992). In this set-up, a participant can have multiple observations. We specify a `(tstart)` and `(tend)` for each event or change in exposure in the sequence. Someone who enters the study January 1, 2000 and experiences an event January 15, 2000 that lasts for 10 days, would first be in in the risk set for 10 days for 1st event, and then would be in the risk set for the second event starting January 25, 2000. For more details on what the dataset looks, see the Appendix B. Each risk interval began when the participant entered or re-entered the study, and ended either when a sick leave episode began (i.e., after an event), a sibling sick leave episode began (change in exposure status), or when the subject was no longer considered at

risk (i.e. censoring). In addition to not contributing time to the risk set when on maternity leave and away from work due to sick leave, participants were removed permanently from the risk set if they emigrated or received disability pensioning.

3.7.7 Sensitivity analysis

We used two general approaches to sensitivity analysis, first to test for bias by fitting the models on a subset of the participants, and second by using a bias formulation. In Paper I, III and IV, we fit the models on subset of people to see whether selection would change results. In Paper I, we ran the analysis on the subset of participants who completed the treadmill test, because it was considered to provide a better quality aerobic fitness measure than the ergometer test. In Paper III, we fit the models using only data from subjects who had registered jobs at age 33, and by using sick leave duration of six weeks or more (>41 days) as cut-offs for exposure and outcome, instead of including all episodes greater than 16 days. In Paper IV, we assessed whether our risk set inclusion criteria may have biased the results by running the analysis on more restrictive subsets of the population. Since our study population in this study was quite young, and many of the participants might still be in school or studying, we were concerned that this might have biased the results. Further, while we accounted for younger sibling's childbirth status, we did not take into account the sibling's childbirth status. We therefore performed the analyses on a subset of participants who had not had children during follow up, and where siblings also had not had children, and where participants had not changed their educational status during follow-up.

In Paper III, we anticipated that unmeasured confounders could have substantial impact on the association between parental and participant sick leave. We therefore ran a sensitivity analysis aimed at assessing the role of unmeasured confounding in bias formulas developed by VanderWeele and Arah (2011). This formulation estimates the characteristics needed for an unmeasured confounder to fully account for the observed association between parent and offspring sick leave.

3.7.8 Test of statistical assumptions

Test of proportionality of hazards in Cox regression models

One of the central assumptions in a Cox regression analysis is the assumption of proportionality of effect over time (Therneau & Grambsch, 2000). In Paper I and IV, where we used Cox regression, we tested the proportionality assumption by examining time trends in the Schoenfeld residuals (Stata's `stphtest`). In Paper IV, many of the confounders violated the assumption of proportionality. For many of the confounders, we included them in the model

as stratifying variables (in Stata, using the `stcox` option `str`) (Therneau & Grambsch, 2000), while age was included in the model by applying a fractional polynomial method to identify a better functional fit (Royston, Ambler, & Sauerbrei, 1999).

Test of no time-dependent effects in causal mediation analysis

The mediation model in a survival context is only specified if effects are non-time dependent. (Lange & Hansen, 2011). To test for time-dependent effects, we fit an Aalen additive hazards model using the `timereg` package in R, which allows all coefficients to be time dependent (Martinussen & Scheike, 2006). For further details on this procedure, see Appendix A. P-values for test for time-dependent effects were above 0.80 and we therefore did not include any time-dependent effects in the final model (Martinussen & Scheike, 2006).

4 MAIN FINDINGS

4.1 Paper I

This paper investigated the association between aerobic fitness in adolescence and musculoskeletal sick leave measured 5 to 15 years later, and the mediating role of educational attainment and work-related factors (i.e., industry and enterprise mean-sick-leave-level). In an unadjusted Cox model, we found that men who, in adolescence, had poor and medium aerobic fitness had substantially higher hazard rates for a musculoskeletal sick leave episode compared to men with high fitness. After adjusting for confounders—which included parental education, intellectual capacity, BMI, and musculoskeletal function (all measured at conscription)—males with poor and medium fitness still had a higher sick leave hazard for non-injury diagnoses compared to males with high aerobic fitness, albeit less so than in the unadjusted model. However, for injury sick leave, the pattern was reversed: males with medium and poor aerobic fitness had a *lower* hazard than males with high fitness. When the mediating variables (educational level, industry, and enterprise mean-sick-leave-level) were included in the model, in a traditional mediation analysis approach, aerobic fitness level was no longer a strong predictor of overall musculoskeletal sick leave hazard. Similarly, the increase in hazard for non-injury sick leave among poor and medium aerobic fitness males, relative to the high aerobic fitness males, had weakened. However, for injury diagnoses, males in medium and poor fitness had an even lower sick leave hazard compared to a model without the mediators.

We further assessed the impact of aerobic fitness on musculoskeletal sick leave, relative to intelligence, parental education level, and other health factors, using a population attributable fraction analysis (PAF). Results suggested that aerobic fitness had very modest impact (PAF 0.060) on sick leave, whereas intellectual capacity and parental education level had the largest impacts (PAFs 0.716 and 0.548, respectively).

A post-hoc test revealed that the association between aerobic fitness and non-injury musculoskeletal sick leave was dependent upon industry (white- versus blue-collar). On an additive scale, poor fitness was more strongly associated with non-injury sick leave among blue-collar workers compared to white-collar workers. That is, on an additive scale, there was an interaction between aerobic fitness and industry.

4.2 Paper II

This paper investigated how much of the adult social gradient in sick leave could be attributed to physical workload while taking into account childhood and adolescent social position and the personality trait neuroticism. Adult social position was associated with the occurrence of one or more spells lasting >16 days during follow-up: the incidence rate, increased from 42.8 in group (I) to 108.5 in group (III) for women and from 24.0 to 69.8 for men. High physical workload, lower childhood social position and high neuroticism were also associated with a higher incidence rate. A change from highest to lowest group in adult social position was, for women, associated with 51.6 (95% confidence interval 24.7–78.5) additional spells per 100,000 person-days at risk, in a model adjusted for early social position and neuroticism. The corresponding rate increase for men was 41.1 (21.4–60.8). Of these additional spells, the proportion mediated through physical workload was, for women, 24% (10–49) and, for men, 30% (10–63). The total effect of adult social position on sick leave was reduced when neuroticism and childhood social position were included in the model; for women in group II, the number of extra spells per day per 100,000 women at risk was reduced by 20% (51.6 versus 63.7), and for those in group III, by 14% (24.3 versus 28.2). For men, the reduction in total effect was substantially lower, 1% and 5% in groups II and III, respectively.

4.3 Paper III

The main aim of the study was to estimate the association between exposure to parental sick leave at age 18 and sick leave risk 15 years later. The one-year sick leave risk in the study population was higher (31.4%) for women than for men (13.1%). Those exposed to parental sick leave had a sick leave risk that was 3.8 percentage points higher than those who were unexposed, irrespective of sex, in models that were unadjusted for confounders. In diagnosis-specific analyses, it became apparent that the association with parental exposure was mainly accounted for by sick leave due to musculoskeletal and psychiatric diagnoses. The elevated risk of sick leave in participants exposed to parental sick leave was moderately reduced after adjustment for parental education and father's income, to 3.4 (2.2 to 4.5) for women, and to 2.8 (2.0 to 3.7) for men. For both women and men, exposure to sick leave episode in same-sex parent was associated with a higher sick leave rate, compared to exposure to sick leave in opposite-sex parent. For women, these associations were not significant, and for men this effect was only significant for all-cause sick leave. Contrary to the study hypothesis, these additive scale associations were of the same magnitude for women and men. For both women and men, diagnosis-specific sick leave was generally higher if exposure was of the same

diagnostic category. The risk of psychiatric sick leave was higher if the parent also experienced a psychiatric sick leave episode. Similarly, the risk of musculoskeletal sick leave was higher if the parent had a musculoskeletal diagnoses, as opposed to other diagnoses, or no sick leave episode. However, the associations were only statistically significant for women. Our sensitivity analysis suggested that an unmeasured confounder associated with a 2.7-fold risk increase in parental sick leave, a 50% risk increase in daughters' sick leave, and a doubled risk increase in sons' sick leave would have fully explained the observed associations between parental and offspring sick leave.

4.4 Paper IV

The aim in this paper was to assess whether the sick leave rate increased following exposure to sibling's sick leave episode. We found that sick leave hazard increases with increasing exposure to sibling sick leave (cumulative number of episodes), more so for males than females. In a model that did not include past sick leave history, but adjusted for all confounders, the hazard ratio in the lowest to highest exposure category ranged from 1.11 (95% CI 1.00–1.23) to 1.30 (95% CI 1.10–1.54) for women, and from 1.25 (95% CI 1.12–1.39) to 1.64 (95% CI 1.37–1.98) for men. When including lagged past sick leave history in the model, these estimates were reduced in all exposure levels, more so for women than for men. In a model restricting the follow-up time from first sick leave episode to recurrent episodes, the pattern of increasing hazard according to increasing sibling exposure was no longer as apparent. Results from the sensitivity analysis showed that the effect estimates in an unadjusted model were weakened moderately when only including individuals not currently in school, whereas they became substantially stronger when only including women who did not give birth while participating in the study.

5 DISCUSSION

5.1 Study validity

5.1.1 Confounding

Unless a confounder is controlled for, it is not possible to determine whether a statistical association observed in data is due to a confounder or a causal association between the exposure and the outcome. To the extent that missing confounders are a problem, this severely limits our ability to infer anything about a causal effect of the exposures of interest. There are several ways in which a study design could give rise to confounding, including not controlling for known confounders, controlling for confounders that are imperfectly measured (Davey Smith, Phillips, & Neaton, 1992; Greenland, 1980) and using a misspecified model (Rothman, Lash, & Greenland, 2008).

Missing variables

In Papers III and IV, we investigated the association between sick leave amongst parent-offspring (Paper III) and older-younger siblings (Paper IV). Important variables here that are likely confounders include norms and attitudes, health, and genetic factors. Though we would have liked to address whether the observed association were causally attributable to social interaction, the absence of these variables makes it very hard to say whether the observed associations were due to confounding. In Paper III, the sensitivity analysis suggests that such confounding would have needed to be quite strong in order to fully explain the results, particularly for men. In Paper IV, we did not perform a similar type of sensitivity analysis, however, we did perform sub-analyses on individuals who had had one sick leave episode during the at-risk period. These individuals were arguably the most “frail” of the group. Within this group, the sibling sick leave association was substantially diminished, but there was overall still some effect present. This might suggest that confounding due to shared propensity was present, and that not including an indicator of frailty would tend to overestimate the sibling association.

In Paper II, we estimated how much of the social gradient in sick leave was mediated through physical workload. Our findings would be biased if there were factors confounding either the direct pathway from social position to sick leave, or the indirect pathway through work (Lange & Hansen, 2011). One possible factor that might be influencing both adult social position (Mensah & Hobcraft, 2008) and sick leave is poor childhood and adolescent health. In our analysis, since we had not included any indicators of early lifecourse health, this would

suggest that the total effect of adult social position on sick leave could be somewhat overestimated. Further, unmeasured poor health in adulthood could also potentially confound the association between physical workload and sick leave, in that people who are experiencing poor health might be more prone to both leave occupations where there is higher physical workload, and would also have a higher risk of sick leave. However, overall the best evidence seems to support that the association between occupation and health is due to a causal effect of the occupational exposures on health, rather than to a selection bias (Clougherty, Souza, & Cullen, 2010).

Mismeasurement and misspecification

A more subtle problem that could lead to confounding, is that factors that have been controlled for, but imperfectly measured can also induce a statistical association that is not causal, a problem referred to as residual confounding due to mismeasurement (Greenland, 1980; Rothman et al., 2008). For instance, in order to assess the impact of aerobic fitness (Paper I) or adult social position (Paper II) on sick leave, as separate from contributions of early childhood conditions, it is critical to adequately control for these factors. We did have rather rich data on a wide array of indicators (e.g., parental: income, education, disability pension, and sick leave), which spanned the entire childhood and adolescent period. However, no measure of social position is assessed without error. Despite the wide array of data we had—or perhaps in part because of it—it was a difficult task to operationalize the data in the most meaningful way. The highest attained education level of your parents clearly does not equal social position during childhood and adolescence. In a rather scathing review of the general epidemiological approaches to the measurement of social phenomena, Oakes and Kaufman note that they remain “remarkably primitive” (2006), and after trying to sort out how to treat 18 years of follow-up data to create the most optimal measure of childhood and social position, it is hard not to agree with him. Our statistical control thus represents an approximation of this construct. In the absence of a measurement that enables us to fully block the statistical association of the confounding pathway, there is likely to be residual confounding. That being said, the reduction in the estimates between the exposures and the outcomes did not appear to be very sensitive to how one operationalized the variables on childhood and adolescent social position (data not shown).

Model specification issues

The form of the model that is fit in order to investigate the associations between exposure and outcome will never be correct, and to the extent that the model is incorrectly specified, the model-based analysis will not completely block confounding paths (Rothman et al., 2008). An example of this is when a confounder is included in the form as a linear term, but the confounding effect may be on a different scale. Including this variable in the model as a linear term will fail to block out the confounding pathway. In this thesis, this issue also is a threat to the validity of the study. For instance, in Paper II and Paper III, we included parental income on a linear scale to account for parental income. It is, however, quite likely that income effects operate on a different scale (Mayer, 2002).

5.1.2 Collider bias

Collider bias occurs when study subjects are selected or become part of the study as a result of a third, unmeasured variable, which is associated with both the exposure and outcome of interest (Hernán et al., 2004). Another way of stating this is that conditioning on a common effect induces an association. This concept can be hard to grasp for many people (Cole, 2002) (present company included), and it is perhaps for this reason that this possibility is often ignored (Glymour, Avendano, & Kawachi, 2014). A collider bias can be the result of sample selection, stratification, or covariate adjustment if some of the covariates are effects of the other independent variables (Hernán et al. 2004). One possible way that we may have induced a collider bias, was by restricting the study participants to only include those who were employed and thus at risk of sick leave. The underlying true health status could be an underlying determinant of both illness, or of being on disability pension. We compensated for this more than most studies by including factors on childhood and adolescent social position, which to some extent takes into consideration these selection factors. Nonetheless, we are unlikely to have fully blocked the colliding bias. It is unlikely that this issue is a major problem in Paper IV, where we include participants from the very start of their employment career. It may be a problem in Papers I–III, where the average age is higher, and where a selection process is more likely to have played out. While causal diagrams are useful tools in identifying possible sources of collider bias, they do not provide information about how to quantify the strength of this bias. The issue of measuring the magnitude of a possible collider bias has received limited attention, though some work suggests that collider biases tends not to be large, except in the presence of strong confounding factors (Greenland, 2003).

Selection bias is a type of collider bias that can result when the study sample is restricted to those who volunteer to participate. In Papers I, III and IV this was not an issue, as we used register data on the entire population. For Paper II, however, our study sample was limited to those who participated in the HUNT3 study. A recent study showed that individuals with low social position, poor health, and higher rates of disability were less likely to participate in HUNT3 (Langhammer et al., 2012). Selection bias could occur in Paper II if there was a factor that tended to influence participation that was also related to the exposure and to the outcome. Underlying health appears to be one such possible factor, though in order to be able to measure the effect of the bias that this would have on our results, one would need to know more about the strengths of the various paths.

Another potential source of collider bias could have resulted from how we defined follow-up time. If someone was included in the risk-set when they were in fact not at risk or not included in the risk-set when they really were at risk, this could have biased the results. First, we did not dynamically track exit from the workforce—that is, while all of the participants had to be employed at the *start* of follow-up, we did not consider if they at some point stopped working. Similarly, women were likely to not be at risk when they were on maternity leave, though this was only accounted for in Paper IV. Allowing for such a discontinuous risk period could have been incorporated very easily in the Papers that employed survival analyses, by using a counting process formulation allowing for discontinuous periods of risk (as I did for Paper IV). In Paper IV, we assessed for the potential impact that incorrect specification of risk time could have led to, and it was shown that the effect estimates actually changed rather dramatically. The results in this paper may have been somewhat extreme though, considering the relatively young age of the participants, their potentially loose ties to the workforce, and the relatively long follow-up period compared to the other studies.

5.1.3 Bias due to misspecification of causal diagrams

Causal diagrams are drawn up based on a priori knowledge of the literature. Whether we controlled for something, or decided not to control for a factor, was based on our causal assumption about the relation between the variables. In Paper II, our causal diagram specifies that the personality trait neuroticism influence attainment of social position and working conditions, rather than the other way around. Our measurement of personality was assessed in adulthood, and was included in the model under the assumption that personality remains relatively fixed (Costa & McCrae, 1992). Recent advances have challenged this perspective

by demonstrating personality changes across the lifespan (Roberts et al., 2006). It could be that personality traits are in part due to social conditions, and events experienced across the lifecourse (Boyce, Wood, Daly, & Sedikides, 2015; Roberts, Caspi, & Moffitt, 2003; Specht, Egloff, & Schmukle, 2011). If this is the case, then controlling for neuroticism measured in adulthood could be blocking effects of social position on sick leave, and our estimates of the total effect of adult social position might be an underestimate of the true causal effects. However, even if it is the case that personality does change in response to the environment, studies of personality changes across the lifecourse suggest that these effects are rather small (Roberts et al., 2006). Further, while the reduction in the effect estimates when controlling for neuroticism was significant when we had not also controlled for childhood and early lifecourse conditions, the additional reduction in estimates was marginal for men, and rather small for women as well, after controlling for childhood and early lifecourse conditions.

Similarly, in our conceptualization of lifestyle factors and depression, we view these as being in part also due to stressful work conditions, rather than being the result of adult social position. By controlling for these lifecourse factors, one might possibly be underestimating the effect of physical workload on sick leave. On the other hand, these factors are probably also in part due to childhood and adolescent conditions, thus by not adjusting for them, we could be overestimating the total effect of adult social position on sick leave through physical workload.

5.1.4 Information bias

Another threat to the study validity could arise from errors in measurements, leading to information bias. Errors of measurement in a variable are non-differential if they are not associated with the true value of any variables in the problem; otherwise the errors are differential. The errors in two variables are said to be independent if the errors in one variable are not associated with the errors in the other; otherwise the errors are said to be dependent (Greenland, 1989).

The measure in this thesis that is, in my opinion, the most problematic is the measure of physical workload, which was used in Paper II. Our index was based on three questions, and these have not been validated in terms of how well they reflect objective physical workload. Despite this limitation, our questions are similar to those used in prior studies, and the results do not deviate by much (Lange & Hansen, 2011). In general, self-report measures could be prone to misclassification. Instead of reporting the objective working conditions, individual traits could lead some people to report the working conditions in a more negative light. The

personality trait neuroticism is one such trait that could lead both to influencing reports of physical workload and also to a higher risk of sick leave. This could lead to dependent misclassification because error in the physical workload variable and error in sick leave reporting could be correlated. In this case, given that people high on neuroticism also have lower adult social position, this would lead to a bias where high physical workload would appear to account more for the social gradient in sick leave than was actually the case. Adjustment for neuroticism could reduce this source of bias (Kristensen, 2005; Podsakoff, MacKenzie, Lee, & Podsakoff, 2003), as it did in our study; however, it should be mentioned again that the reduction in estimates once childhood and adolescent social position were taken into account were rather small. However, the issue regarding subjective reporting raises the overarching question about what we really are interested in measuring. Individuals will differ in how they perceive things, and it is not immediately apparent that this deviation is something that should be factored out. It could be that it is their perception of working conditions, rather than the objective levels of them that influences their sick leave behavior. As such, it is not a bias, but a vulnerability factor that moderates the effect of a given exposure on the risk of sick leave, and one that we should try to understand so we can provide individually targeted interventions.

There is perhaps also a risk of misclassification in regard to the parental income variable. In our study, we used pensionable income as an indicator of income. However, income in itself is not necessarily indicative of financial standing (Mayer, 2002). It seems plausible that pensionable income is a poor indicator of risk for those who are rich in other ways, for instance as measured by wealth. It does not immediately seem plausible that the risk of sick leave is similarly misclassified according to this variable—that is, that people with higher economic standing would have a different likelihood of being misclassified with regard to the outcome, sick leave. However, being misclassified as being at risk, when one in fact is not, seems more likely. One could imagine that people with low social position would be more likely to become unemployed during the follow-up period or that women with high income would take longer maternity leaves, which would lead to a differential misclassification of time at risk.

5.1.5 Study size

We had low power in Paper IV in the sub-analysis restricted to participants who had had one prior event. Similarly, we collapsed the exposure groups, due to very wide confidence intervals in the higher exposure categories. We may, therefore, have missed some interesting patterns. We could have had a much larger sample if we had not limited the sample study to only include sibships of size two, or if we had used a longer follow-up period. The choice of only including sibships of size two was a result of the analytic and conceptual difficulty of trying to disentangle who was influencing whom. Initially, we identified the eldest and second-eldest sibling in a family and that were born between 1967 and 1976, regardless of whether they had more siblings born during that decade, or before or after. However, in this sample we would be underestimating potential influence from other, unmeasured, siblings. We could have included all siblings, regardless of sibship size, though it appeared methodologically difficult to model the increasingly complex past histories of sibling sick leave. The choice of following them up for five years was based on the desire to evaluate a sibling effect when siblings might be the most likely to influence one another—shortly after they have been living together (or possibly while they are still living together). Another approach would have been to look at time-dependent effects over the lifecourse—maybe we would have found that sibling associations were higher during early employment, and then decreasing over time as other peers become more important.

In Paper II, small power was also an issue that led us to use only three adult social position groups, leaving a more fine-grained pattern undetected. Further, it is possible that small power left us unable to detect an interaction between neuroticism and physical workload, and between adult social position and physical workload.

5.1.6 Assumption of the statistical tests

Assumption of proportional hazards (Paper I and II)

First and foremost, an assumption of the Cox proportional hazard model is that of non-informative censoring. What this means, is that the probability of being censored must not depend upon the underlying condition being studied (i.e., sick leave). In Papers I and IV, participants were censored if they emigrated, died, or went on disability pension. The latter two censoring events could obviously be related to an underlying disease that could also be influencing sick leave risk. However, very few participants were actually censored during follow-up, suggesting that such a possible violation would not have notably impacted the results.

The second central assumption in a Cox regression analysis is that of proportionality of effect over time (Therneau & Grambsch, 2000). In Paper I, there did not appear to be problems with proportionality. In Paper IV, however, there were quite obvious violations of proportionality for the exposure variable (sibling sick leave) and for many of the covariates. We also found that parental education violated the proportional hazard assumption, even though that was not the case in Paper I, which is perhaps a bit surprising. However, participants were followed from the very first entry into the job market, so their age was overall younger than participants in Paper I. It is plausible that the age-dependent effect of parental education is merely stronger at the younger age, when participants are first entering, and perhaps also exiting, the workforce. Another possible explanation is that the social gradient in sick leave is especially strong for those individuals who have recurring episodes of sick leave. In Paper I, where we only studied time to first event, these individuals leave the risk set fairly early in the study. In Paper IV, these individuals were followed once their first sick leave episode was over; one may therefore, in a sense, have greater power to observe the effect of parental social position over time.

With the exception of age, we included the confounders that violated the proportional hazard assumption in the model as stratifying variables. In this context, stratifying means that the variables are added as control variables to the model, which circumvents the restriction of the proportional hazard assumption. While this was a convenient way of handling the assumption of the model, we were not able to obtain any effect estimates using this approach, which would have been an advantage. It was challenging to fit a dynamic Cox model without violating the proportional hazards assumption. An alternative may have been to fit an additive hazards model, like we did in Paper II, which estimates time-varying effects and does not impose such a strict assumption (Aalen et al., 2008b).

Classic regression mediation analysis

The assumptions of this analysis were outlined in great detail in section 3.7.4. In Paper I, we used the traditional epidemiological approach to assess mediation, derived from the Baron-Kenny approach, in a Cox regression framework. Given that this approach is restricted to linear models, with additive effects, the approach we took thus violates this assumption. Further, Paper I showed that there was an interaction between the exposure (aerobic fitness) and the mediator (industry); that is, the effect of the exposure on sick leave was modified by industry level. This is another assumption laid out in the original framework that appears to have been violated in our analysis. Therefore, it seems reasonable to interpret these findings

with some caution. Several mediation methods have, subsequent to the publishing of Paper I, been developed in the counterfactual framework that allows for interaction between the exposure and the mediator, for outcomes with dichotomous or count outcomes (Valeri & Vanderweele, 2013). The mediation analysis method developed by Lange and Hansen (2011) for survival outcomes, also allows for interactions, though the technique cannot, at this time, be employed using standard software.

Assumptions of causal mediation analysis

For these estimates to be unbiased, there are five main assumptions, which need to hold, as outlined in the paper by Lange and Hansen (2011). The first three of these assumptions relate to the exchangeability assumption in causal inference (Hernán & Robins, 2016), and specify that all of the pathways in the model must not be confounded. The fourth assumption is a modified version of Pearl's (2001) identifiability assumption, and states that the exposure has its effect on the outcome and mediator through two non-intertwined causal pathways. This would, for instance, be violated if there was a factor influenced by adult social position that both influenced physical workload and sick leave propensity. Arguably, physical health is one such factor that could potentially violate this assumption. That is, if physical health is in part a result of adult social position, which could in turn influence occupational selection and level of physical workload, then it would seem that this condition was violated. However, given the data that we had, it was difficult to assess whether such effects were present. Last, the method relies on the assumption of consistency, which implies that the outcome would not change if the exposure and mediator were set to the values they would "naturally" take.

5.1.7 Interpretation of population attributable fraction

In Paper I, we quantified the contribution of various risk factors on the outcome by estimating the population attributable fraction (PAF). In a causal sense, this is the proportional reduction of the outcome that would occur in a population if exposure to the risk factor were eliminated. A causal explanation of the combined poor/medium aerobic fitness level PAF of 0.06 would be that the average population risk of musculoskeletal sick leave would be reduced by 6% if the whole population had been subject to physical training intervention that resulted in a global high aerobic fitness level. Concluding that the musculoskeletal sick leave risk would be 6% lower in the whole population than what was actually observed if all had a sick leave risk similar to the high fitness group, would be a non-causal explanation that would fit these observational data better.

The PAF estimate is dependent on not only the strength of the exposure–outcome association, but also the prevalence of the exposure in the population. The consequence of this, is that cut-off value for the categorization of an exposure (risk factor) can have a major impact on the PAF magnitudes. One example is intellectual capacity, whose PAF was 0.716 (Paper 1, Table 4). This was based upon the assumption that the whole population would have had a sick leave risk similar to the small proportion of men with maximum stanine score of 9 at conscription. A more realistic scenario could be that the one third of the population with intellectual capacity score lower than the mean score of 5 (stanine score 1–4) would have had the absence risk of the two thirds with stanine scores 5–9. The resulting PAF with these assumptions was considerably lower than 0.716 (PAF 0.263; 95% CI 0.254–0.272). The 0.06 PAF for aerobic fitness (Paper 1, Table 4) was based upon the aerobic fitness classification made by the conscript test personnel, and we therefore did not have the opportunity to assess the changes in PAF magnitude using a different cut-off point.

5.1.8 Generalizability

Sick leave rates vary within geographical region, according to economic changes and according to the welfare system. As such, the generalizability to other countries and settings may be limited (Voss, Floderus, & Diderichsen, 2001). In Paper II, our population was restricted to participants residing in Nord-Trøndelag and participating in HUNT3. A recent study showed that individuals with low social position, poor health, and higher rates of disability were less likely to participate in HUNT3 (Langhammer et al., 2012). This might tend to provide lower estimates of sick leave rates and underestimate the social gradient in sick leave. Further, our study participants were restricted to people living in the county of Nord-Trøndelag, so our findings may not be generalizable to other populations.

5.2 Comparison with other studies and interpretations

5.2.1 Aerobic fitness and sick leave

Poor aerobic fitness in adolescence could be a factor predisposing one for sick leave in later life. This pathway may potentially act through education and work-related factors, so poor aerobic fitness is one step on a trajectory towards sick leave propensity later in leave. Identifying such early risk factors, and pathways by which they operate, is important for possible interventions. We found that aerobic fitness in adolescence was moderately associated with sick leave 5 to 15 years later, when controlled for several confounders. The only study we are aware of that has investigated the association between aerobic fitness and

sick leave, is a cross-sectional study by Lindén (1969). He found that poor aerobic fitness was associated with an increased risk of sick leave amongst customs officers, though not amongst fire fighters. In that the latter group is selected based on having good health, which might have induced a collider bias, the results of his study seem compatible with ours.

Our findings are compatible with several longitudinal studies that have found relatively weak associations between physical activity and sick leave (Eriksen & Bruusgaard, 2002; Holtermann et al., 2012; Kyröläinen et al., 2008; Lahti et al., 2010b, 2012; van Amelsvoort et al., 2006; van den Heuvel, Heinrich, et al., 2005). Similar results have been found for physical activity and disability pension (Fimland et al., 2015; Lahti, Rahkonen, Lahelma, & Laaksonen, 2013). However, participants in these studies range in age from early 20s to retirement, and the analyses were not performed for different age groups, thus limiting the comparability to our study. Studies assessing the importance of physical fitness in adolescence on later health outcomes are more limited. Sacker and Cable (2006) found that physical activity measured in adolescence predicted self-reported health 15 years later in one cohort (1958), but not the other (1970).

Our finding of an increase in sick leave hazard for the non-injury group, and a decrease in the injury group, was novel. There is some evidence that individuals with good aerobic fitness are at increased risk for non-occupational injuries compared to individuals with poor aerobic fitness (Heir & Eide, 1997; Mattila, Kuronen, & Pihlajamäki, 2007).

Confounding role of intelligence, parental education, BMI and physical functioning

The observed association between adolescent aerobic fitness and sick leave was substantially reduced when early lifecourse factors were included in the model. The studies that have investigated an association between physical activity and sick leave also found similar results when including BMI and physical factors in the models (Amlani & Munir, 2014). To my knowledge, our study is the first to also consider intelligence and parental education when evaluating the link between aerobic fitness and sick leave. The inclusion of parental education and intelligence were the strongest confounders for aerobic fitness and sick leave, and the PAF analysis suggested that their relative contribution to sick leave was also substantially greater than aerobic fitness. This finding is compatible with prior studies showing that intelligence is both correlated to physical activity in adolescence (Deary, Whalley, Batty, & Starr, 2006), sick leave (Henderson et al., 2009), and disability pension (Lundin, Sörberg Wallin, Falkstedt, Allebeck, & Hemmingsson, 2015). It also further supports the strong evidence that childhood conditions are important for later outcomes, including physical

fitness (Stea, Wandel, Mansoor, Uglem, & Frølich, 2009), sick leave (Bäckman & Palme, 1998), and disability pension (Gravseth et al., 2007).

Mediation and interaction: education and work-place factors

The mediation analysis revealed that education level and work-related factors appeared to mediate the link between adolescent aerobic fitness and sick leave. It was a novel finding that the influence of the mediating pathway had opposite signs for injury and non-injury sick leave: for non-injury sick leave risk, the pathway through the mediator served to increase the sick leave risk for males with poor and medium aerobic fitness, compared to males with high aerobic fitness. For injury sick leave, on the other hand, the pathway through the mediator served to decrease the risk of sick leave amongst males with medium or poor fitness, compared to high fitness. The result was that for non-injury sick leave (where poor or medium fitness leads to higher sick leave) the direct effect was reduced, or was closer to the null, in a model that included the mediators. However, in a model that included the mediators for injury sick leave, the direct effect became stronger, or moved away from the null. We separately studied whether there was an effect measure modification between aerobic fitness, and work characteristics (defined as white vs. blue collar), finding that poor fitness had a stronger effect on sick leave among blue-collars than among white-collars.

To my knowledge, few have investigated the association between adolescent physical fitness, education, work-related characteristics, and sick leave. A study by Lahti et al. (2010b) investigated whether the association between physical fitness and sick leave would be fully accounted for by BMI and social position. When they included social position and BMI, the protective effect of high physical fitness was still present, but was no longer statistically significant. They measured all of the variables at the same time (except sick leave), and as such, the study does not lend itself to a causal interpretation. In addition, the study participants were middle aged, ranging from 40 to 60. A study by Holtermann et al. (2012) investigated the role of what they call “occupational physical activity” and leisure time physical activity on sick leave. What they refer to as “occupational physical activity” (i.e., “you are mainly sedentary”, “you have heavy physical work”) is what we have referred to as physical workload. They found that leisure time activity is protective, while occupational physical activity is detrimental. Unfortunately, they only present models where all covariates have been controlled for, and do not show crude models, making it difficult to assess whether the mediators are weakening or strengthening the observed associations between physical

activity and sick leave (that is, whether there is an interaction effect between exposure and mediators).

Overall, these findings are in line with a trajectory concept of sick leave, in which parental education, intelligence, and BMI predisposes one for poor aerobic fitness, and people with poor aerobic fitness are in turn more likely to end up with lower educational attainment and in blue-collar jobs, which in turn increases the risk of musculoskeletal sick leave.

Inference

Our study was able to control for a wide array of individual characteristics, and early lifecourse factors. However, there were important variables that we did not have data on, and which could confound the study, including adolescent physical health. We therefore cannot rule out that the observed association was due to unmeasured confounding. Further, as discussed earlier, the traditional Baron-Kenny analysis does not always lead to valid results when applied to a model where there are interactions between the exposure and the mediator, and where the model produces non-linear effect estimates. In our analysis, there appeared to be an interaction between the exposure and the mediator. As such, the exact interpretation of these findings is a bit unclear. At the time this analysis was conducted, a mediation analysis in the counterfactual framework had not been developed yet for survival outcomes. Further, this procedure was, and probably still is, the standard method for mediation for both Cox and Poisson models. VanderWeele (2015) points out that the Baron-Kenny approach can give valid results under some conditions, depending upon the prevalence of the outcome and type of model. For the Cox proportional hazards model, the traditional epidemiological approach can provide a valid estimate of whether a mediator is present, though only if the outcome is relatively rare.

5.2.2 Adult social position and sick leave, mediating role of physical workload

The role of work factors in linking adult social position to sick leave and health in general has been a topic of much research. The findings from our study replicates findings from other research showing that the social gradient in sick leave is reduced when factoring in the role of the physical exposures at work (Christensen et al., 2008; Kaikkonen et al., 2015; Laaksonen, Piha, Rahkonen, Martikainen, & Lahelma, 2010; Lange & Hansen, 2011; Sterud & Johannessen, 2014). Direct comparison with these studies is difficult, due to the different analytic approaches in measuring mediation. The paper by Lange and Hansen (2011) is the only other study we are aware of that estimates the mediating effect of physical work environment in a survival context with a causal interpretation. In their study, they found that

the proportion mediated via physical work environment ranged from 24–48% for men and 26–71% for women, which is slightly higher than what we found. However, direct comparison is difficult due to the use of different measures of adult social position and physical work environment. Another aspect of our study that makes direct comparison with other studies difficult is that most of them controlled for other aspects of the working environment, health at baseline, and lifestyle factors. The relation between working conditions and other lifecourse factors could quite likely be the result of a complex causal chain, whereby working conditions may be prohibitive of a healthy lifestyle, and reduced health resulting from a poor lifestyle may influence the ability to handle physical workload. Therefore, while several lifecourse factors were assessed in the HUNT3 study, we chose not to control for them because they could in part be a result of coping with high physical workload, rather than a pathway operating directly from adult social position to sick leave.

Confounding role of childhood social position and neuroticism

We made a unique contribution to this literature in that we were able to include childhood and adolescent social position and neuroticism in assessing the mediating role of physical workload on sick leave. Our study suggests that childhood and adolescent social position and neuroticism are important confounders of the relation between adult social position and sick leave, and by taking into account these early factors, we get a more conservative estimate of the rate increase attributable to physical workload. The finding that the total number of extra sick leave episodes in group III compared to group I are reduced when factoring in childhood and adolescent social position and neuroticism is compatible with a lifecourse perspective, whereby adult social position and health is influenced by earlier factors in life. This interpretation is in line with several studies showing that social position early in life is important for health (Power, Manor, & Matthews, 1999) and sick leave (Kristensen et al., 2007), even while accounting for adult social position. Fewer studies have investigated the role of personality as an early lifecourse factor accounting for the attainment of adult social position and health outcomes, but there is evidence from a study by Hampson et al. (2007) that personality traits can in part explain the social gradient in self-reported health through its influence on both education and health-promoting behaviors. Similarly, it is compatible with the study by Henderson et al. (2012) that suggest that temperament in childhood was predictive of sick leave, though this effect was negligible after education, intelligence, and working conditions were taken into account.

Inference

This study has the advantage of using a mediation analysis that has a causal interpretation, and that is well defined for survival outcomes. However, causal inference still relies on several untestable assumptions. This includes that none of the pathways in the mediation analysis are confounded by unmeasured factors. Another central issue is that the study assumes that personality traits measured in adulthood are representative of personality in childhood and adolescence, which is consistent with the tendency to view personality as relatively fixed (Costa & McCrae, 1992). Recent advances have challenged this perspective by demonstrating personality changes across the lifespan (Roberts et al., 2006). Further, these personality changes have been linked to environmental influences (Kandler, 2012), including adverse experiences at the workplace (Caspi, Wright, Moffitt, & Silva, 1998). As such, personality could in part be a result of adverse conditions throughout the lifecourse, rather than the ultimate cause of them. If this is the case, then including neuroticism might tend to underestimate the role of adult social position and physical workload on sick leave. Another challenging aspect regarding neuroticism is that it is strongly linked to depression (Kendler, Kuhn, & Prescott, 2004). If depression is in part a result of high physical workload, then by controlling for neuroticism, we could in part be blocking a causal pathway from physical workload to sick leave which would lead to an underestimation of the true effect of physical workload. Lastly, it seems there is still a need to identify alternative pathways that are linking adult social position to sick leave, and to determine whether individual characteristics may lead some individuals to be more susceptible to these mediating factors.

5.2.3 Social interaction

Social interaction as an explanation for sick leave has been of interests concerning neighbors, colleagues, and family members. If it is the case that sick leave is in part due to social influence within the family, then interventions that reduced sick leave in one family member would also reduce the sick leave rate in the rest of the family. We performed two studies that explored this possible explanation, a sibling study and an intergenerational study, though neither study enabled causal inference regarding the putative role of social interaction as an explanation for sick leave. The two studies used rather different methodologies, the main difference being that in the sibling study we included an indicator of frailty to try to account for propensity to sick leave. In the intergenerational study, we found that there was an association between exposure to parental sick leave at age 18 and 1-year sick leave risk 15 years later. In the sibling study, using a dynamic Cox model with time-dependent exposure,

we found an increase in sick leave risk following exposure to older sibling's sick leave, and that the association was stronger with increasing exposure. The association was weakly reduced when we included past sick leave in the model as an indicator of individual frailty. However, when restricting the analysis to time-from-first-sick-leave to recurrent sick leave episodes, the effect became much stronger the pattern was less clear.

Prior evidence of sick leave social interaction

Prior studies on sick leave have primarily focused on neighbors (Hesselius et al., 2008; Lindbeck et al., 2008; Markussen & Røed, 2015) and colleagues (Bokenblom & Ekblad, 2007; Hesselius et al., 2009; Ichino & Maggi, 2000; Johansson et al., 2014), and have found mixed evidence of a social interaction using a wide array of methodological approaches, as reviewed in section 1.5. Only two studies have assessed sick leave within families, including one twin studies (Gjerde et al., 2013) and one population based fixed-effects study (Markussen & Røed, 2015). The study by Gjerde et al. used a twin design to determine genetic versus environment contribution to long term sick leave in a population of nearly 8000 twins, from 1998 through 2008 (2013). However, as pointed out by Gjerde (2014), this type of analysis may be hampered by low power (Neale & Rijsdijk, 2005). The study by Markussen and Røed (2015) assessed whether social interaction within neighborhoods and families could account for sick leave and other types of absence from work (e.g., disability pension) by using a fixed effects methodology. They found a moderate social interaction effect, which was weaker the more distantly related the family members were. However, as they mention, they did not take into account family propensity to sick leave, which means that it is hard to rule out whether the similarities in sick leave hazards amongst family members are caused by a shared genetic propensity to sick leave. Overall, these two studies appear to be compatible with the findings from our sibling study, in that a study that considers genetic frailty (Gjerde et al., 2013) did not find evidence of a family effect, whereas a study that did not, did find evidence of a sibling effect (Markussen & Røed, 2015). While the study by Markussen and Røed is comparable to the approach used in Paper IV, in that it uses time-dependent exposures, and assesses the increase in hazard following a change in exposure, it is not very comparable to the intergenerational study which focuses on sick leave exposure 15 years prior.

Whereas few studies on sick leave interactions within the family have been done, there is somewhat more evidence regarding intergenerational effects within disability pension and welfare usage, which was reviewed in Section 1.5. Overall the link between parental and

offspring disability pension rate has been established in three studies (Bratberg et al., 2012; Dahl et al., 2013; Gravseth et al., 2007), though causal evidence is perhaps only convincing in the study by Dahl et al (2013). Findings from this study suggest a relatively strong intergenerational influence of parental disability pension on offspring, an effect that appeared to be irrespective of whether or not the offspring was still residing at home at the time parental disability pension was approved.

Gender differences

As of now, it is still unexplained why women have a higher sick leave risk than men (Kostøl & Telle, 2011). Our hypothesis was that sex differences in intergenerational transmission might be stronger among mothers and daughters compared to fathers and sons, though our findings were not supportive of this. A few other studies have investigated sex. Bokenblom and Ekblad (2007) found a positive and significant group effect amongst colleagues, though only within sex. Men influenced other men, and women influenced other women, though they did not influence one another. Similarly, Johansson, Karimi and Nilsson (2014) identified the same pattern among teachers: men were only affected by their male peers, and women were only affected by their female peers. While we did not detect a sex-specific pattern of intergenerational transmission, it seems quite possible that our measure of parental sick leave exposure was really too crude to be able to fully distinguish between sex-specific parent sick leave. While we did measure sick leave exposure during the year participants were 18, they may obviously have been exposed to parental sick leave in the time preceding this, that was unmeasured by us. Thus, while we were unable to identify differences in the risk of being exposed to sick leave in a parent of the same, versus opposite, sex, it seems premature to rule out that such a difference may in fact exist.

Inference on intergenerational effect

We used an observational design, in which we tried to account for correlated effects (or a shared propensity to sick leave) in parent and offspring by controlling for a host of confounding variables. The general problem of reverse causality was unlikely to be a large problem in this design, where participants were rather young at the time of exposure, at a time when they would have been unlikely to influence parental sick leave propensity. The fundamental problem is knowing whether the observed associations are due to a causal effect of exposure on the outcome, that is, a social interaction effect, or whether other factors are creating the observed association. Additionally, we did not control for parental disability pensioning, which potentially could influence sick leave behavior. We can therefore not rule

out that the observed association is due to some other factors, like genes, shared social environment, or other factors contributing to parents and offspring having a similar propensity to sick leave. Results from our sensitivity analysis suggest that such confounding would have to be relatively strong in order to explain the observed association.

Inference on sibling effect

In Paper IV, we fit a dynamic Cox regression model to assess whether exposure to sick leave in an older sibling was associated with increased sick leave rate. Exposure and past sick leave history were included in the model as lagged, time-dependent variables. Our study showed that exposure to an older sibling's sick leave was followed by an increased sick leave rate and that by introducing past sick leave into the model this association was slightly reduced. The only study we know that explicitly tests for sibling interaction, a twin study by Gjerde et al. (2013), found no indication of a sibling interaction. However, their study included a longer time-span, and did not take into account the dynamic nature of sibling interaction. The divergent estimates in the analyses restricted to participants with a past history of sick leave, compared to the full sample, can be accounted for by two competing interpretations. One possibility is that sibling effect estimates were *confounded* by unidentified propensity to sick leave. However, when this frailty was to some extent controlled for, as it was in the analysis for individuals who had had one episode of sick leave, the sibling exposure association was strongly diminished. Another possible interpretation is that there was a causal effect of sibling exposure on sick leave rate—that is, that there is a social interaction leading to a change in younger sibling's behavior—but that this interaction effect is strongest for the first sick leave episode. The idea that an older sibling plays an important social role in the development of risk has been substantiated with respect to many health outcomes (Bricker et al., 2006; D'Amico & Fromme, 1997; Monstad et al., 2011). That such a social interaction effect may be strongest for the first instance of sick leave is compatible with a learning mechanism account of why there might be a social interaction effect. However, our study does not allow us to say whether the association was causally attributable to social interaction, or whether the association was due to unmeasured confounding. Despite this limitation, the application of a dynamic Cox model allowed us to include the development of sick leave into the model as a covariate, which was essential in disclosing exposure-outcome heterogeneity.

5.3 Future research

The goal for epidemiologists is to gain knowledge about what causes sick leave, or other outcomes, rather than just identifying statistical associations. With this goal in mind, it seems wise for future research to focus on designs, methods, and the use of data sets that makes this more likely.

The use of register data to study sick leave seems very promising, as this is data with full national coverage that is not sensitive to reporting bias. Our study shows that early lifecourse factors were confounders of all of the associations that we studied, and as such it would be wise for others to consider these factors in their analyses. One of the weaknesses of our study was that we did not have very good measurements of health through the lifecourse, leaving this as a possible confounder in all of the studies. Further, having access to a dataset in which several of the factors were measured at multiple time-points in the lifecourse would have enabled us to identify in which direction the causal arrows were pointing. Perhaps, for instance, one option would be to link register data to other health studies with multiple waves. One example might be the other HUNT studies (Krokstad et al., 2013), where data has been collected over several waves starting in adolescence. Further, using variables on working conditions that are of higher quality will improve future studies.

The pathway through physical workload represents one of many possible targets for an intervention, and the finding that a substantial gradient persists after taking into account the role of physical workload suggests that other causal pathways, such as through psychosocial work factors and the range of lifestyle factors, are also linking adult social position and sick leave. Future studies should also consider whether there might be interaction between social position and work factors—that is, whether people with lower social position both get a worse work environment, and react more strongly to said work environment. Thus future studies ought to ensure that they have great enough power to be able to detect such possible interactions. Developments in mediation analysis rooted in a causal framework have made advances that enables the analysis of multiple mediating pathways and interactions (VanderWeele, 2015). Future studies would benefit from applying these mediation analyses. Our mediation analysis in Paper II focused on all-cause sick leave; another interesting avenue to pursue is the mediating role of different type of work factors on diagnosis-specific sick leave; it seems plausible that hazard of psychiatric diagnoses might be more sensitive to psychosocial stressors, whereas musculoskeletal diagnoses might be more sensitive to a hazardous physical environment.

Another finding from this study is that survival analysis appears useful to detect some patterns that are obscured in methods that do not allow for time-dependent covariates and effects, and where the discontinuous risk is not accounted for. In our study (Paper IV), removing women from study when on maternity leave had a rather pronounced effect on the estimates, though few researchers appear to take the discontinuity of risk into account in their analyses. Our study also suggests that future studies could benefit from exploring whether there are time-dependent or time-varying effects in the study. The benefit of using a survival approach is that one can incorporate these changes into the model directly, whereas other studies tend to measure at baseline and then follow up for a given number of years. It would be interesting to use this approach to reanalyze some of the studies of the effect of the number of children in the household, which have generally not found any evidence of an increased sick leave risk of having children, but which have not used time-dependent approaches to measuring number of children.

Social interaction as a cause of sick leave is an interesting avenue to pursue, though the methodological challenges of identifying such an effect is daunting. Nonetheless, it seems that future studies in epidemiology ought to use designs which enable causal inference. New work in causal inference has also focused on methods for identifying social interaction effects (spill-over effects), which also seems like an avenue worth pursuing (VanderWeele, 2015). It has been suggested that epidemiologists ought to use the instrumental variable approach used by economists (Glymour et al., 2014). While this pseudo-randomized approach is useful in identifying causal effects, it does not shed any light on the mechanisms linking treatment to outcome. Thus, if there indeed are social interaction effects amongst family members, other methods would be needed in order to address through what pathways such effects operate. Perhaps some network analysis approach would be more suitable, though this would probably require the use of data not available from national registries.

5.4 Conclusion

Our study provides further evidence of the importance of considering early lifecourse factors when studying sick leave, as opposed to focusing solely on contemporary, or “downstream”, factors. This approach enabled us to identify novel pathways linking conditions partly determined already in childhood and adolescence. We found that males with poor and medium aerobic fitness in adolescence were at a moderately higher risk of adult musculoskeletal sick leave, and this appeared to be due, in part, to educational and work trajectories. However, given that this analysis was performed using a traditional mediation

analysis, in which the analytic assumptions were not met, an exact interpretation of these findings is hard to give. Another novel finding is that we identified neuroticism and early childhood and adolescent conditions as confounders of adult social position, physical workload, and sick leave. By including these “downstream” factors in the analysis, the total effect of adult social position on sick leave was reduced. Further, we were able to quantify the natural direct and indirect effects using a method that allowed for causally interpretable results. This thesis has also added to the growing evidence of an aggregated sick leave risk within families. We are the first to show that exposure to parental sick leave in adolescence is a risk factor for sick leave, and that this association was not, contrary to our hypothesis, stronger for mothers-daughters than for father-sons. Further, we found that exposure to an older sibling’s sick leave episode is temporally followed by an increase in the younger sibling’s sick leave hazard, and that there appeared to be a dose-response relationship, with increasing sibling exposure leading to even higher sick leave hazard. However, the dose-response relationship was strongly diminished when a measure of frailty was taken into account, suggesting that methods that do not account for this are likely to be biased. Attempting to unravel the complex etiology of sick leave throughout the lifecourse, with time-dependent effects, shared genetic frailty, and complex causal networks, provided several methodological difficulties. Due to the methodological challenges, we could not determine whether the observed familial associations were causally attributable to social interaction. Further, we could not rule out unmeasured confounding in any of the studies. Understanding the causal links throughout the lifecourse seems an important goal nonetheless, in that interventions targeted earlier in the lifecourse could potentially have longer-lasting impacts. Future studies would benefit from considering early lifecourse factors as possible confounders when studying contemporary risk factors, and should also study alternative pathways, with possible interactions, linking childhood early life conditions to sick leave. Last, registry data, possibly linked to richer sources of health data throughout the lifecourse, is likely to be a trove for addressing more complex causal pathways using newly developed methods for causal inference.

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APPENDIX

A. Appendix: Implementation of causal mediation analysis in R

A detailed overview of implementation of Lange and Hansen (2011) model can be found in their online eAppendix (<http://links.lww.com/EDE/A476>). The Additive hazards model is fit using the package "timereg" in R. I will here give a brief overview of the steps along with examples of code.

The data frame "datasetF", for all females in the study, contained the following variables:

Event Sick leave episode (yes/no)	HuntMaritSt Marital status
TimeToFirstSA Time to event or censoring	(unmarried/married/divorced)
wSEP Adult SEP levels for women (I, II, III)	RevParEdu Parental education level
physSum Physical workload index	ParentsAvInc Parental income (quintiles)
Neuroticism Neuroticism	ParentalDP Parental disability at age 18 (yes/no)
BirthYear Age at baseline	

The *OLS model* for the mediator was fit using the following command:

```
ols_mediator = glm(physSum ~factor(wSEP3) + Neuroticism + BirthYear  
+ factor(HuntMaritSt) + factor(RevParEdu) + ParentsAvInc +  
factor(ParentalDP) , data=datasetF)  
summary(ols_mediator)
```

Summary(ols_mediator) displays the parameter estimates for the linear regression of physical workload on adult workload displayed in Table 2, Paper II. The second step involved fitting an *Aalen's additive hazards survival model* in the timereg package:

```
library(timereg)  
aalen_outcome = aalen(Surv(TimeToFirstSA,Event) ~ factor(wSEP3) +  
physSum + Neuroticism + BirthYear + factor(RevParEdu),  
data=datasetF, robust=T)  
summary(aalen_outcome, digits=7)
```

The summary (aalen_outcome) tests the four hypotheses that none of the coefficients need to be time dependent. Interaction terms were included by arguments like

⁸physSum*Neuroticism. As none of the terms tested were significant, they were not included in the final model. The simplified model (that is, with no time-dependent effects) was estimated by the following command:

```
library(timereg)
aalen_outcome = aalen(Surv(TimeToFirstSA,Event) ~
  const(factor(wSEP3)) + const(physSum) + const(Neuroticism) +
  const(BirthYear) + const(factor(RevParEdu)), data=datasetF,
  robust=T)
summary(aalen_outcome, digits=7)
```

The command `summary(aalen_outcome)` displays the parameter estimates (including direct effect of adult social position on sick leave, with 95 % CI) shown in Table 3, Paper II.

To obtain estimates of IE, TE and IE/TE we implemented the following code, due to Lange and Hansen, with 95% confidence intervals estimated by simulation:

```
#####SES level II v I
IE_SEP = as.numeric(ols_mediator$coefficients["factor(wSEP3)2"]) *
  as.numeric(aalen_outcome$gamma["const(physSum)",])
#gamma=coefficients
IE_SEP
DE_SEP = as.numeric(aalen_outcome$gamma["const(factor(wSEP3)2",])
DE_SEP

#Confidence intervals for IE, TE and Q=IE/TE computed by simulation:
CI_comp(
  mean_lambda1 =
  as.numeric(aalen_outcome$gamma["const(factor(wSEP3)2",]),
  mean_lambda3 = as.numeric(aalen_outcome$gamma["const(physSum)",]),
  covar11 =
  aalen_outcome$var.gamma["const(factor(wSEP3)2", "const(factor(wSEP3)
)2"],
  covar12 =
  aalen_outcome$var.gamma["const(factor(wSEP3)2", "const(physSum)"],
  covar22 =
  aalen_outcome$var.gamma["const(physSum)", "const(physSum)"],
  mean_alpha =
  as.numeric(ols_mediator$coefficients["factor(wSEP3)2"]),
  var_alpha =
  summary(ols_mediator)$coefficients["factor(wSEP3)2", "Std. Error"]^2
)
```

```

#####SES level III v I
IE_SEP = as.numeric(ols_mediator$coefficients["factor(wSEP3)3"]) *
as.numeric(aalen_outcome$gamma["const(physSum)",])
#gamma=coefficients
IE_SEP
DE_SEP = as.numeric(aalen_outcome$gamma["const(factor(wSEP3))3",])
DE_SEP

#Confidence intervals for IE, TE and Q=IE/TE computed by simulation:
CI_comp(
  mean_lambda1 =
as.numeric(aalen_outcome$gamma["const(factor(wSEP3))3",]),
  mean_lambda3 = as.numeric(aalen_outcome$gamma["const(physSum)",]),
  covar11 =
aalen_outcome$var.gamma["const(factor(wSEP3))3","const(factor(wSEP3)
)3"],
  covar12 =
aalen_outcome$var.gamma["const(factor(wSEP3))3","const(physSum)"],
  covar22 =
aalen_outcome$var.gamma["const(physSum)","const(physSum)"],
  mean_alpha =
as.numeric(ols_mediator$coefficients["factor(wSEP3)3"]),
  var_alpha =
summary(ols_mediator)$coefficients["factor(wSEP3)3","Std. Error"]^2
)

```

B. Appendix: Description of the dataset, Stata's *stset* procedure, and sample code

In order to fit the data to the model, we need to create an appropriate data set. Going from having event-history data for a set of two siblings, to one in which the data is ready for analysis is a multistep process that is quite involved. The first step is to link the event-history files, so that all of the older sibling's events are recorded in relation to the younger sibling. The second step involves going from an event-history format to a survival format. The third step is to perform the *stset* procedure so the data can be analyzed using *stcox* in Stata. The last step is to specify the model and run the analysis. To give the reader a sense of what the dataset looks like, I will here show an example of what the data might look like for one cohort member who has been linked to event-histories of an older sibling. I will skip the first two steps as I have followed the general procedures that are well described elsewhere (e.g., the book by Cleves et al.), and start with a description of what the dataset looks like in survival format, once the siblings' event-histories have been linked and turned into survival format.

Example of dataset in survival format

The dataset shown in *Table B-1* displays the event histories of a study participant with ID 1, represented by eight risk set periods. The first row represents the period from the beginning of the study (January 1, 1992) to January 1, 1997, the date the older sibling is employed (event=9). The second row represents the date from older sibling employment (January 1, 1997), to the date the study participant is employed (i.e., the person who is under observation) on April 15, 1998 (event=8). This is the date where the participant enters the study (start of 5-year follow up). End of follow-up will then be five years from that date, or April 14, 2003 (as indicated in the variable *stopp5*). The third row then represents the date of start of follow-up (April 15, 1998), and ends on August 7, 2002 when the study participant has a sick leave episode (event=1). The fourth row starts on the day that the sick leave episode begins (August 7, 2002), and ends on the date that the sick leave episode ends on October 25, 2002 (event=2). This risk period is not to be included in the risk set, since the participant is not at risk of a sick leave episode. The fifth row shows the risk period from when the participant returns to work from the sick leave episode (October 25, 2002), and ends on November 19, 2002 due to sibling having a sick leave episode (event=3). Note also how the past sick leave covariate (*cumSA*) has gone from 0 to 1, to indicate that the person has had one sick leave episode in the previous risk period. The sixth row spans from November 19, 2002–March 17, 2007, ending because the participant has another sick leave episode (event=1). Now the sibling

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exposure variable (*cumExp*) has increased from 0 to 1, to indicate that the participant has been exposed to 1 episode of sibling sick leave up until this point in time. The seventh row, March 17, 2007–May 1, 2007, represents the duration of the sick leave episode; the historic sick leave episode has increased from 1 in the previous row to 2, to incorporate that the participant has had one more sick leave episode. The last row shows time from re-entry after sick leave episode to the end of the study period (May 1, 2007–December 31, 2009). The next step is to run the Stata procedure *stset* on the data.

Table B-1. An example of the dataset in survival format, for cohort member with ID 1

Row	ID	begin	end	event	atrisk	cumSA	cumExp	trunc	stopp5
1	1	01jan1992	01jan1997	9	1	0	0	0	.
2	1	01jan1997	15apr1998	8	2	0	0	0	14apr2003
3	1	15apr1998	07aug2002	1	2	0	0	0	14apr2003
4	1	07aug2002	25oct2002	2	2	1	0	1	14apr2003
5	1	25oct2002	19nov2002	3	2	1	0	0	14apr2003
6	1	19nov2002	17mar2007	1	2	1	1	0	14apr2003
7	1	17mar2007	01may2007	2	2	2	1	1	14apr2003
8	1	01may2007	31dec2009		2	2	1	0	14apr2003

Variable description:

- ID** Identification number
- begin** Starting date of risk period (or beginning of the study period, January 1, 1992)
- end** End date of risk period – indicates date of an event, or end of the study period (December 31, 2009)
- event** Event occurring on the date “end”: 1=Sick leave, 2=End sick leave, 3=Sibling sick leave, 4=Birth of child, 5=Change in marital status, 6=Emigration/Death/Disability pension, 7=Emigration/Death/Disability pension sibling, 8=Employment (from 4th month), 9=Employment start sibling (from 4th month)
- atrisk** Indicates when person should enter study: 0=neither sibling is employed, 1=one sibling only is employed, 2=both siblings are employed.
- cumSA** Cumulative number of sick leave episodes (counting starts from beginning of study period)
- cumExp** Cumulative number of sibling sick leave episodes (counting from beginning of study period)
- trunc** Equal to 1 if observation is to be excluded from analysis, due to index being on sick leave or presumed maternity leave
- stopp5** time variable indicating date that study participant has been under observation for 5 years

Running Stata's stset command

The function *stset* in Stata defines variables named **_t0**, **_t1**, **_d** and **_st**. The variables **_t0** and **_t1** record the time span in analysis time units (t) for each record. **_d** records the outcome at the end of the span and is set to 1 if the time span ends in a failure (i.e., have an event) and 0 if it does not. **_st** records whether this observation is relevant (or to be used) in the current analysis. For each observation, the variable contains 1 if the observation is to be used and 0 if it is to be ignored. The function *stset* allows for a wide array of options, which are described in great detail in the book by Cleves et al. (Cleves et al., 2008) and which I have used as a guide.

Specifying analysis time I want analysis time to be 0 when employment starts for both siblings, and to start ticking from there. The **origin()** option can change the time scale. The variable **atrisk** listed in the variable description, has the value 2 on the date when both siblings are employed (for four months). We can make the time start ticking when by including **origin(atrisk==2)** in the *stset* command.

Specifying when subjects enter the analysis I want participants to enter at the onset of risk. Stata's default is that subjects enter at analysis time $t=0$ (as specified by **origin()**), or if the earliest records in the data are after that, subjects enter then. In our case we want enter when both siblings are employed, **enter(atrisk==2)**.

Specifying when subjects exit from the analysis By default, a person would exit when they fail (have an event). We have multiple observations per person, and do not want participants to exit upon failure. The option **exit()** controls when a person can exit. I want them to exit when either the participant or the sibling dies, emigrates, or goes on disability pension. This option can either be specified by a variable, or by a given time variable. The time I want individuals to exit is indicated by the variable **stopp5**, at which point five years of observation have passed. The option **exit(event=6 7 time stopp5)** will thus remove participants from risk set if event is 6 or 7, or when the t equals **stopp5**.

Convenience options We want to exclude observations when the participant is not actually at risk for a sick leave episode, which is indicated by the variable **trunc**. The option **if()** solves this issue. The option **if(trunc=1)** will omit rows in which person is currently having a sick leave episode.

Specifying the begin-of-span variable To specify the beginning of the span, one can use the option **time0()**. You need to specify this option if you have time gaps in your data and you do not want *stset* to assume that you do not. This is the case for us as time is discontinuous due to the trunk option.

The Stata *stset* command thus ends up looking like this:

```
stset end, if (trunc!=1) failure(event==1) id(family) origin(atrisk==2) ///  
time0(begin) enter(atrisk==2) exit(event==6 7 time stopp5)
```

After the *stset* procedure, the four variables `_t0`, `_t1`, `_d`, and `_st` have been added to the dataset. The resulting dataset is shown in *Table B-2*. The time span from the first two rows (in grey) are ignored, as both siblings are not yet employed (indicated by `_st` being 0 for both rows). The participant is at risk on the first yellow row (row three), and the time variable `_t0` starts at 0 on this date (and `_st` is 1). The first risk period ends with a failure, indicated by `_d` being 1. The subsequent row (row four) is not included in the risk set due to the participant being on sick leave during that time period, which is indicated by `_st` being 0. The next risk period (row five) is again included, though the time variable starts from 1654, rather than the starting from the end of the previously included risk period (1575). The period between 1575 and 1654 has thus not been included in the risk set. The risk period on row 6 is included up to `_t1=1825`, which is when the participant has been followed-up for five years. The time span in the two remaining rows (row 7 and 8) are not included in risk set.

Table B-2. Dataset in survival format including *sfset* variables

Row	ID	begin	end	event	atrisk	cumSA	cumExp	trunc	stopp5	_t0	_t1	_d	_st
1	1	01jan1992	01jan1997	9	1	0	0	0	0
2	1	01jan1997	15apr1998	8	2	0	0	0	14apr2003	.	.	.	0
3	1	15apr1998	07aug2002	1	2	0	0	0	14apr2003	0	1575	1	1
4	1	07aug2002	25oct2002	2	2	1	0	1	14apr2003	.	.	.	0
5	1	25oct2002	19nov2002	3	2	1	0	0	14apr2003	1654	1679	0	1
6	1	19nov2002	17mar2007	1	2	1	1	0	14apr2003	1679	1825	0	1
7	1	17mar2007	01may2007	2	2	2	1	1	14apr2003	.	.	.	0
8	1	01may2007	31dec2009		2	2	1	0	14apr2003	.	.	.	0



Example stcox code

Table 3, model 2:

```
stcox i.cumSA i.cumExp mAge1 mAge2 i.marital i.mstat2 if male==1, str(year cat5entry  
s_cat5entry edu mpDP) efron robust
```

