Chapter 1

Why family matters: an introduction

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I

Baked the day she suddenly dropped dead
we chew it slowly that last apple pie.

Shocked into sleeplessness you're scared of bed.
We never could talk much, and now don't try.

You're like book ends, the pair of you, she'd say,
Hog that grate, say nothing, sit, sleep, stare…

The 'scholar' me, you, worn out on poor pay,
only our silence made us seem a pair.

Not as good for staring in, blue gas,
too regular each bud, each yellow spike.

At night you need my company to pass
and she not here to tell us we're alike!

You're life's all shattered into smithereens.

Back in our silences and sullen looks,
for all the Scotch we drink, what's still between 's
not the thirty or so years, but books, books, books

II

The stone's too full. The wording must be terse.
There's scarcely room to carve the FLORENCE on it—

Come on, it's not as if we're wanting verse.
It's not as if we're wanting a whole sonnet!

After tumblers of neat Johnny Walker
(I think that both of us we're on our third)
you said you'd always been a clumsy talker
and couldn't find another, shorter word
for 'beloved' or for 'wife' in the inscription,
but not too clumsy that you can't still cut:

You're supposed to be the bright boy at description
and you can't tell them what the fuck to put!

I've got to find the right words on my own.

I've got the envelope that he'd been scrawling,
mis-spelt, mawkish, stylistically appalling
but I can't squeeze more love into their stone.

Book Ends by Tony Harrison[1]

Not surprisingly, family is central to art and literature as well as science. Tony Harrison's early poems in *The Loiners*[2] (a slang name for someone from Leeds) and *From the School of Eloquence and Other Poems*[1] describe the indelible effects of parents, extended family, social class, and the interrelationships of these, on one's wellbeing.[3] Those anthologies provide a very compelling and vivid image of the many ways in which families matter to all aspects of life. In *Book Ends*, the recently deceased mother recognized the unique bond between father and son, whereas Harrison describes the distance between them resulting from his social mobility and education—*'books, books, books'* – but for all his education and way with words he cannot give the poetry he craves to his father's love for his mother. In a more recent poem—*Rice-Paper Man*[4]—Harrison describes his anguish as he tries to cope with his son's severe mental illness and again the complexity of family relationships and how they influence health and wellbeing of all family members are clear.

The contributors to this book may not have the poetic skills of Tony Harrison, but they do have the knowledge and understanding to describe the requirements to set-up, maintain, analyse, and correctly interpret family-based life course epidemiology studies, which is what we hope the book will provide for its readers.

1.1 Time to raise the bar and push life course epidemiology to provide more causal answers

It is just over one decade since the first edition of the first life course book was published,[5] and since that support for a life course approach to epidemiology has increased considerably. In that original book the editors noted that 'The prevailing aetiological model for adult chronic disease emphasizes adult risk factors.'[5] (page 3) The focus on adult risk factors for chronic complex diseases, such as cardiovascular disease, cancer, and mental health problems, can be thought of as a degenerative aetiological model, since it is, on the whole, identifying factors associated with time and speed of degeneration in structure and function.

This degenerative model pays little attention to processes that lead up to the peak or optimal phenotypic state—usually seen to be a feature of early adulthood, such as the greatest lung volume (usually attained in late adolescence/early adulthood in humans), peak vascular function (usually attained in late adolescence in humans) or peak bone mass (usually attained post-puberty in humans). However, over the last 2–3 decades the degenerative model has been supplemented by approaches that view the development of anatomic, physiological and psychological systems as key to later disease susceptibility. This approach to understanding disease processes recognizes the importance of peak phenotypic states (in addition to how rapidly one degenerates from this peak) as having important relevance to the likelihood of developing complex chronic diseases. These development models of disease causation—that echo, but with increased biological motivation, much earlier discussions of determinants of health[6]—together with the degenerative model are at the heart of life course epidemiology. Over the last decade epidemiology has greatly expanded the evidence for the importance of a developmental approach to understanding the aetiology of chronic complex diseases (see, for example, many of the chapters in the second edition of the first book in the life course series[7–9]). However, very little work has really taken the life

course approach to its limit of combining understanding of both development and degeneration of systems and function in order to develop appropriate methods for improving population health.

Life course epidemiology is '*the study of the effects on health and health related outcomes of biological (including genetic), environmental and social exposures during gestation, infancy, childhood, adolescence, adulthood and across generations*.'[10] As Diana Kuh and colleagues have noted,[10] this definition does not mean that all epidemiology can be defined as life course, rather a life course approach aims to understand the relevance of different exposures, occurring at different times in the life course on later health. Thus, explicit in the definition is the need to combine understanding of factors that affect both development and degeneration. Furthermore, understanding different life course models is key to using life course epidemiology to inform public health policy and improve population health.[10] Finally, to improve population health the life course approach also has to go beyond merely describing associations, to determining whether these associations are truly causal and, if so, whether in relation to timing of the exposure it can or should be modified.

For example, a recent large Danish record linkage study demonstrated an association between greater body mass index (BMI) in childhood (measured between ages 7–13 years) and future risk of coronary heart disease (CHD) mortality.[11] The risk was linear across childhood BMI distribution, but the magnitude of the association increased with older age at measurement. In girls there was no association until BMI measured at age 10 or older and in both sexes the association was strongest for BMI measured at age 13 years.[11] The strengthening of the effect with older age at measurement might mean that much of the association of childhood BMI with adult CHD is mediated via adult BMI (with the tracking of childhood BMI into adulthood), but the study was unable to determine whether that was the case. If this were the case then interventions aimed at reducing BMI in adulthood might be equally as beneficial for reducing CHD risk as any interventions aimed at preventing childhood obesity. It is also possible that this association is explained by obesity in childhood causing permanent changes in metabolic and vascular function that do not revert to normal even if weight is lost between childhood and adulthood. If this were the case then clearly interventions aimed at preventing the development of childhood obesity would be paramount. Finally it is possible that the association is not causal but explained by confounding, for example by socioeconomic background. To translate the findings from the Danish record linkage study into relevant public health messages a much fuller picture of the life course epidemiology linking childhood BMI to adult CHD is required:

- To what extent is the association causal or explained by confounding, by for example family socioeconomic background and lifestyle characteristics?
- If causal, to what extent is the association mediated by adult obesity and its associated adverse metabolic and vascular effects?
- If causal, to what extent is the association mediated by changes to metabolism and vasculature in childhood that are permanent even if the child were to lose weight?
- If causal, and importantly mediated by both childhood and adult metabolic and vascular changes, is prevention of obesity easier to achieve by interventions in childhood or adulthood; or is there no difference by age at which one tries to prevent obesity?
- What are the main determinants of greater BMI/obesity in childhood (or adulthood)?
- What are the best ways of preventing obesity in childhood and adulthood; do the methods and their cost-effectiveness differ for children and adults?
- Would family-based interventions, aimed at preventing obesity in all family members (adults and children), provide the most effective and cost-effective means of preventing obesity and hence CHD?

This list of questions is not exhaustive, but they serve to illustrate that the association of an exposure during early life (a period of development) and a disease outcome in later life, whilst illustrating that some of the important concepts of a life course approach, raises many more questions that it can answer. No single study will answer all of these questions but as a number of existing birth cohorts, such as the UK 1946[12] and 1958[13] birth cohorts, Perinatal Collaborative Study from US,[14] the Aberdeen children of the 1950s cohort,[15] and the Danish Metropolit cohort,[16] move into adulthood and have very rich prospectively collected data during periods of development and degeneration, we have to start pushing for investigators to publish papers that do engage with a fuller life course picture. This will require more sophisticated statistical approaches than the multivariable regression models commonly used in associational epidemiology and the correct interpretation of these models. Several of these issues are discussed in the last life course book to be published in this series–*Epidemiological methods in life course research*[17]—and also in Chapters 10–12 in this book. Family-based approaches can help with some issues of causality and possibly with timing of different exposures. These too, require use of appropriate statistical techniques and a clear understanding of the theoretical underpinning of different family studies in order to interpret correctly their results. This book aims to describe the key ways in which family-based studies can enhance life course epidemiology, but also highlight the importance of correctly conducting and interpreting the results from these studies.

1.2 The use of family-based studies in life course epidemiology

Families are at the heart of life course epidemiology. Its very definition necessarily involves mothers, who are clearly central to exposures during gestation and family members (parents/care-givers and siblings) who will influence one's experience of childhood and adolescence. Once one is an adult, partners, pregnancies (for females) and offspring (including whether one does or does not have offspring) will shape health and health related behaviours. Furthermore, the definition explicitly includes genetic factors and the intergenerational transfer of characteristics.

There are three potential ways in which family-based studies (i.e. those in which data are purposefully collected on more than one family member) might contribute to life course epidemiology. First, family will directly affect one's health by determining many of the biological, environmental and social exposures across the life course. Secondly, different family members will exert their impact on one's health by different degrees at different times in the life course, and hence detailed studies of family influences could help to understand the importance of timing of exposures across the life course. Lastly, comparing relationships within and between different family members can help to clarify the mechanisms underlying associations in life course studies and help to determine causality.

1.2.1 Direct influences of family on health across the life course

At all stages of the life course behaviours in family members seem to influence health and health related behaviours in the index individual. This is perhaps most notable during fetal development when maternal behaviours and her health and physiology influence normal fetal growth and development in ways that can have lasting effects. Maternal smoking during pregnancy is one of the main causes of low birth weight in industrialized countries.[18] Maternal use of high doses of diethyl-stilbestrol (DES) during pregnancy (a treatment given to pregnant women from the 1930s to 70s, in the mistaken belief that it would reduce pregnancy loss) is now known to cause menstrual and reproductive disorders and vaginal cancer in daughters,[19–25] and is associated with reproductive disorders in sons,[20] and menstrual and reproductive disorders in grand-daughters.[26]

Maternal pregnancy use of the drug thalidomide, a potent anti-emetic used by pregnant women during the 1950s and 60s to combat morning sickness, provides a further example of the direct effect of maternal exposures on the developing fetus.[27] Thalidomide caused infants to be born with phocomelia and other permanent limb deformities, particularly when mothers had taken the drug during the sensitive period of limb development between days 20–40 of gestation.[27]

Families also affect one's health and behaviours at other times in the life course. A mother's ability and decision to breast feed or not affects morbidity and mortality in infancy and in the longer term having been breast fed is causally related to higher cognitive ability at mean age 6.5 years in a large randomized controlled trial.[28] There is evidence that different family members influence health behaviours and outcomes in later life. Though, interestingly for health behaviours there is some evidence that spouses influence each other more than parents influence children or siblings influences each other. For example, in the National Heart, Lung and Blood Institute Family Heart study familial associations for behaviours—alcohol consumption, exercise and smoking—were strongest for spouses and notably weaker for parent-offspring and sibling correlations.[29] Similarly, in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort there was only weak associations between parental physical activity and their offspring's physical activity at age 11–12.[30] By contrast familial correlations of high and low density lipoprotein cholesterol were stronger for 'blood relatives' (parent-child and siblings) than they were for spouses in the National Heart, Lung and Blood Institute Family Heart study.[29] This suggests that family correlations of these phenotypes are influenced importantly by genetic factors and less so by shared familial behaviours.

The moderate to strong associations for health related behaviours between spouses have been demonstrated in other studies,[31, 32] and these findings formed the basis of a recently evaluated intervention to reduce cardiovascular disease in high risk individuals that targeted both the high risk adults (those with a previous cardiovascular event or predicted with ≥5% risk during the next 10 years to have an event based on risk factor assessment) and their partners for lifestyle changes.[33] At 1 year follow-up higher proportions of those at high risk in the intervention arm, compared to the standard treatment arm, had met goals for dietary saturated fat intake, oily fish intake, fruit and vegetable intake, physical activity, weight loss, smoking cessation and blood pressure. Differences in lipids, HbA_{1C} and medication use (statins, antiplatelets, beta-blockers, and ACE inhibiters) did not differ markedly between the two groups.[33] The differences in health related behaviours in the patients were matched by similar changes in their partners. The effect of spouses on one's health is also demonstrated by the increased risk of all-cause, cardiovascular, cancer and accident and violent mortality in spouses following the death of their spouse.[34]

Several of the chapters in this book, notably Chapter 14, which describes the relevance of family-based studies to understanding the life course epidemiology of mental health, describe other ways in which family members and family relationships directly affect one's health across the whole life course.

1.2.2 Using family influences to understand the importance of timing in life course epidemiology

As noted above it is important in life course epidemiology to go beyond simple associations to understanding whether or not timing matters with respect to interventions to improve population health. For example, if an exposure during a developmental period in early life is causally related to a later health outcome, but only through strong tracking of that exposure during the life

course, one would need to consider when in the life course it is most effective to remove the exposure. If it is easier to effectively remove it in adulthood, than childhood, then interventions in adulthood would be most appropriate.

Since our exposure to different family members changes over the life course family studies could help to understand whether exposures at different stages of the life course are important or not. As described in Chapter 2 this has been most exploited with respect to intrauterine exposures. Thus, maternal behaviours during pregnancy have been used to explore the fetal origins of several disease outcomes (i.e. the intrauterine period as a sensitive or critical period for certain risk factors). However, care is required in correctly interpreting these studies, and several recent examples that have shown, for example, similar magnitudes of association between maternal and paternal smoking at the time of pregnancy and future offspring obesity and blood pressure,[35, 36] and similar magnitudes of association of modest maternal and paternal alcohol consumption at the time of pregnancy and future IQ levels in offspring,[37] illustrate that it can be misleading to assume that a maternal behaviour during pregnancy (particularly one that is unlikely to be solely done in pregnancy) is having an offspring effect via intrauterine mechanisms. These issues are discussed in more detail in Chapter 2.

Changes in levels of familial associations at different times of the life course can also give some clues about aetiological subgroups. For example, the within monozygotic twins association for coronary heart disease weakens considerably with increasing age, such that the relative risk for a co-twin dying of coronary heart disease if the other twin has already died of coronary heart disease before age 65 is 15.0, but decreases monotonically with increasing age of the first heart disease death in a twin pair to being consistent with the null once this occurs at age 80 or older.[38] These findings suggest that premature heart disease is more likely to be related to a genetic aetiology than coronary disease occurring at older ages.

1.2.3 Using family comparisons to understand mechanisms underlying

For a large part this book is concerned with the correct conduct and interpretation of family-based studies—intergenerational studies, sibling studies, and twin studies—to help understand causal mechanisms in life course epidemiology. As will be seen in the subsequent chapters, use of family-based studies for this purpose necessarily requires an understanding of the direct effects of family on health and an understanding of how exposure to different family members changes over the life course. Our hope is that the book will demonstrate the potential of these studies and thus motivate researchers to use them more. It would be nice to write a second edition in 10 years' time and be able to demonstrate that life course epidemiology really has moved on in terms of causal understanding and translation to effective interventions for improving population health, and that family-based studies have made major contributions to this development.

1.3 The aims of this book

Family data and specific family-based studies (intergenerational, sibling, and twin studies) could make important contributions to a full life course understanding of health and disease. However, understanding the underlying assumptions of these studies and hence the inferences that can be drawn from them is complex. Furthermore, there are issues relating to study design, including how to obtain valid and reliable data from family members, ensuring correct linkage between members of the same family and indeed how to define members of the same family, and issues relating to the statistical analysis of family-based studies that are not well understood.

The aim of this book is to provide in one volume the knowledge and skills required to design, analyse, and correctly interpret family-based studies.

Our hope is that this book will explain what family-based studies can tell us about life course epidemiology; provide practical guidance on how to set-up and maintain birth cohorts for completing family-based studies in life course epidemiology; describe how to undertake appropriate statistical analyses of family-based studies and correctly interpret results from these analyses; and provide examples that illustrate the ways in which family-based studies can enhance our understanding life course epidemiology.

The book is divided into four sections that correspond to these aims. **Part I** describes the theoretical underpinning for the use of different family-based studies (including intergenerational, twin, and sibling studies) in life course epidemiology, by detailing the assumptions underlying these studies and the inferences and understanding that can be gained from each type of study. **Part II** describes the practicalities of undertaking family-based studies, including undertaking such studies in low and middle income countries and issues relating to use of proxy informants (e.g. parents providing information on children and vice versa or siblings providing information about each other) in family-based studies. **Part III** describes appropriate statistical approaches for family-based studies. Our aim in this part is to provide statistical guidance in non-technical language as well as providing relevant algebra and programming syntax, so that individuals from different backgrounds will find relevant information for undertaking appropriate analyses, checking model assumptions, and correctly interpreting of the statistical output. Finally, **Part IV** provides examples of how family-based studies have been used in understanding the life course epidemiology of cardiovascular disease, mental health, and reproductive health. These examples are intended to illustrate the relevance of family-based studies, not only to these areas, but also more generally to the whole of life course epidemiology. In our final chapter we discuss ideas for further uses of family-based studies in life course epidemiology.

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