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Genetic and Environmental Contributions to Trajectories of Depressive Symptoms

University of Bristol
School of Geographical Sciences

A thesis submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Social Science and Law

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Abstract

Depression is a complex mental health disorder, predicted to be the highest global burden of disease by 2030. Research has examined the antecedents of adolescent depression in order to limit and prevent depression from occurring. However, depression during this phase of development is multifactorial and variability in depression is characterised by important features such as the age of onset, chronicity and severity. Identifying these features, and how depressive mood changes across time along with potential risk factors may aid in our understanding of the nature of adolescent depression and help develop new interventions and treatments.

This thesis uses longitudinal methods to explore the nature of trajectories of depressive symptoms and examine how genetic, and early environmental risk factors contribute to trajectories of depressive symptoms across adolescence and young adulthood in a UK population based cohort, the Avon Longitudinal Study of Parents and Children. Using group-based and multilevel frameworks, trajectories of depressive symptoms are estimated across adolescence and then various risk factors are explored to investigate how these trajectories change across time.

Genetic risk for depression, childhood bullying, female sex and childhood trauma are all associated with less favourable trajectories of depressive symptoms. Importantly, several risk factors are associated with changes in depression across time, and not just at certain stages of development. This implies they have lasting effects and that it may be possible to identify when particular risk factors are having their greatest effect on later depression.

This work provides further evidence that depressive symptoms across adolescence to young adulthood are complex and associated with both genetic and environmental contributions. Examining depressive symptoms across time within a longitudinal framework provides a powerful opportunity to examine the nature of depression in more detail than in previous research.

Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: ..... **DATE:** .....

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Contents

1 Introduction **17**
- 1.1 Background and rationale . . . 17
- 1.2 Previous research, key limitations and potential solutions . . . 18
- 1.3 Thesis aims and objectives . . . 21
- 1.4 Thesis structure . . . 23
- 1.5 List of publications and submissions . . . 26
- 1.6 My contribution to this research . . . 27

2 A Review on The Nature of Trajectories of Depressive Symptoms from Childhood to Young Adulthood: Methods, Predictors and Future Considerations **29**
- 2.1 Introduction and chapter objectives . . . 29
- 2.2 Chapter abstract . . . 30
- 2.3 Introduction . . . 30
  - 2.3.1 Trajectories of depressive symptoms from childhood to young Adulthood . . . 31
  - 2.3.2 Existing limitations and considerations of trajectories of depressive symptoms research . . . 31
  - 2.3.3 The current review . . . 32
- 2.4 Statistical methods for examining trajectories of depressive symptoms 32
  - 2.4.1 Methodological variation . . . 32
  - 2.4.2 Multiple-subpopulation trajectories . . . 34
  - 2.4.3 Population-averaged trajectories . . . 36
  - 2.4.4 Methods summary . . . 37
- 2.5 Previous findings on trajectories of depressive symptoms between childhood and young adulthood . . . 40
  - 2.5.1 Number of trajectories . . . 40
  - 2.5.2 Characteristics of trajectories . . . 41
  - 2.5.3 Shapes of trajectories . . . 42
  - 2.5.4 Nature of Trajectories . . . 42
  - 2.5.5 Risk factors for trajectories of depressive symptoms between childhood and young adulthood . . . 43
- 2.6 Limitations in previous studies and considerations for future research 50
  - 2.6.1 Small duration of follow-up and lack of waves of data collection 50
  - 2.6.2 Size matters . . . 51
  - 2.6.3 Future research . . . 51
- 2.7 Conclusions . . . 53
- 2.8 Chapter summary . . . 53

3 Data and Methods **55**
3.1 Chapter introduction . . . 55
3.2 Data source . . . 55
3.2.1 Depressive symptoms . . . 57
3.3 Data considerations . . . 64
3.4 Statistical methods . . . 68
3.4.1 Multilevel growth-curve models . . . 68
3.4.2 Growth mixture modelling . . . 70
3.5 Chapter summary . . . 71

4 Identifying Trajectories of Depressive Symptoms Across Adolescence and Young Adulthood **73**
4.1 Chapter outline . . . 73
4.2 Introduction . . . 74
4.3 Methods . . . 76
4.3.1 Growth mixture modelling . . . 78
4.3.2 Missing data . . . 79
4.4 Results . . . 80
4.4.1 Sample . . . 80
4.4.2 Multilevel growth-curve models . . . 80
4.4.3 Growth mixture models . . . 85
4.5 Discussion . . . 89
4.5.1 Comparisons with previous research . . . 89
4.5.2 Population-averaged trajectories in ALSPAC . . . 89
4.5.3 Multiple-subpopulations in ALSPAC . . . 90
4.5.4 Similarities and opposites . . . 91
4.6 Chapter summary . . . 92

5 Genetic and Environmental Risk Factors Associated with Trajectories of Depressive Symptoms from Adolescence to Young Adulthood **93**
5.1 Chapter outline . . . 93
5.2 Chapter abstract . . . 94
5.3 Introduction . . . 95
5.4 Methods . . . 97
5.4.1 Sample . . . 97
5.4.2 Depressive symptoms . . . 98
5.4.3 Risk factors . . . 98
5.4.4 Confounders . . . 100
5.4.5 Statistical analysis - growth mixture modelling . . . 101
5.4.6 Missing data . . . 101
5.5 Results . . . 101
5.5.1 Trajectories of depressive symptoms . . . 102
5.5.2 Association between risk factors and trajectories of depressive symptoms . . . 102
5.6 Discussion . . . 107
5.6.1 Strengths and limitations . . . 109
5.7 Conclusions . . . 110
5.8 Chapter summary . . . 110

6 Sex Differences and Trajectories of Depressive Symptoms from Childhood to Young Adulthood 113
6.1 Chapter outline . . . 113
6.2 Chapter abstract . . . 114
6.3 Introduction . . . 115
6.3.1 The current study . . . 117
6.4 Methods . . . 118
6.4.1 Participants . . . 118
6.4.2 Measures . . . 118
6.4.3 Statistical methods . . . 120
6.5 Results . . . 122
6.5.1 Trajectories of depressive symptoms . . . 122
6.5.2 Age of Peak Velocity and Age at Maximum Depressive Symptoms . . . 125
6.5.3 Depressive Symptoms Score at Age of Peak Velocity and at Age of Maximum Point of Depressive Symptoms . . . 125
6.5.4 Missing Data and Sensitivity Analysis . . . 125
6.6 Discussion . . . 126
6.7 Conclusion . . . 131
6.8 Chapter summary . . . 132

7 Childhood Trauma and Trajectories of Depressive Symptoms Across Adolescence 133
7.1 Chapter outline . . . 133
7.2 Chapter abstract . . . 134
7.3 Introduction . . . 135
7.4 Methods . . . 139
7.4.1 Sample . . . 139
7.4.2 Measures . . . 139
7.5 Results . . . 141
7.5.1 Sample characteristics . . . 141
7.5.2 Direct model output vs alternative model parameterisation . . . 143
7.5.3 Association between any trauma and trajectories of depressive symptoms . . . 143
7.5.4 Association between the number of types of trauma and trajectories of depressive symptoms . . . 147
7.5.5 Comparing depressive symptom scores at different ages . . . 149
7.6 Discussion . . . 152
7.6.1 Main findings . . . 152
7.6.2 Considerations . . . 154
7.6.3 Limitations and future research . . . 155
7.7 Conclusions . . . 156
7.8 Chapter summary . . . 157

8 Association Between Polygenic Risk and Trajectories of Depressive Symptoms 159
8.1 Chapter outline . . . 159
8.2 Chapter abstract . . . 160
8.3 Introduction . . . 161

8.4 Methods . . . 163
8.4.1 Sample . . . 163
8.4.2 Depressive Symptoms . . . 163
8.4.3 Polygenic risk score for depressive symptoms . . . 163
8.4.4 Statistical analysis . . . 164
8.4.5 Missing data . . . 165
8.5 Results . . . 165
8.5.1 Sample characteristics . . . 165
8.5.2 Association between depressive symptoms polygenic risk score and depressive symptoms using cross-sectional analysis . . . 168
8.5.3 Association between depressive symptoms polygenic risk score and trajectories of depressive symptoms . . . 170
8.5.4 Comparisons between higher and lower genetic risk at various ages . . . 170
8.6 Discussion . . . 173
8.7 Conclusions . . . 176
8.8 Chapter summary . . . 176

9 Conclusions **177**
9.1 Overview . . . 177
9.2 Contributions to the literature . . . 178
9.2.1 Identifying trajectories of depressive symptoms across adolescence . . . 178
9.2.2 Genetic and environmental risk factors associated with trajectories of depressive symptoms from adolescence to young adulthood . . . 179
9.2.3 Sex differences and trajectories of depressive symptoms from childhood to young adulthood: the role of critical points . . . 180
9.2.4 Early childhood trauma and trajectories of depressive symptoms 180
9.2.5 Association between polygenic risk and trajectories of depressive symptoms . . . 181
9.3 Local considerations . . . 182
9.3.1 Comparing methodological approaches . . . 182
9.3.2 Varying effect sizes . . . 183
9.3.3 Benefited interpretation and translation . . . 184
9.4 Global considerations . . . 185
9.4.1 Viable data? . . . 185
9.4.2 Repeated measures benefits . . . 185
9.4.3 Public health and policy implications for growth-curve research 186
9.5 Limitations . . . 187
9.6 Future research . . . 190
9.7 Concluding remarks . . . 191

Bibliography **193**

A Appendix **219**

List of Figures

1.1 Cross-sectional vs repeated-measures approaches 19

2.1 Growth modelling approaches 33

3.1 ALSPAC 56
3.2 Descriptives of the SMFQ 59
3.3 Histograms of the SMFQ 61
3.4 Descriptives of the SMFQ (complete case) 64
3.5 Nested data 68

4.1 Comparisons between MLMs 83
4.2 Quartic polynomial model in ALSPAC 84
4.3 5 trajectories identified from the GMM 86
4.4 Observed trajectories from the GMM 87
4.5 Predicted trajectories from the GMM 88

5.1 Histogram of the DS PRS 99
5.2 5 trajectories from the GMM 103
5.3 Association between risk factors and trajectories (figure) 106

6.1 Cubic polynomial trajectories by sex 124

7.1 Unadjusted association between childhood traumas and trajectories of depressive symptoms 145
7.2 Adjusted association between childhood traumas and trajectories of depressive symptoms 146

8.1 Association between depressive symptoms and depressive symptoms across adolescence 172

List of Tables

1.1 Thesis research objectives 24

2.1 Summary of growth-curve approaches 39

3.1 List of SMFQ questions 58
3.2 Descriptive statistics and reliability 60
3.3 Correlations between the SMFQ 63
3.4 Participant demographics 1 66
3.5 Participant demographics 2 67

4.1 Model estimates between trajectories 81
4.2 Comparison between polynomial models 82
4.3 Comparison between trajectory groups in the growth mixture model . 85

5.1 Unadjusted multivariate associations between risk factors and trajectories of depressive symptoms (table) 104
5.2 Adjusted associations between risk factors and trajectories of depressive symptoms (table) 105

6.1 Descriptive statistics of SMFQ by sex 119
6.2 Cubic polynomial model estimates 123
6.3 Parameter estimates and trajectories from the cubic polynomial model 123
6.4 Trajectory features from the cubic polynomial model 125

7.1 Participant demographics for the number of traumas 142
7.2 Childhood trauma estimates 144
7.3 Associations between number of traumas and trajectories of depressive symptoms 148
7.4 Comparisons between any trauma trajectories and depressive symptoms scores at various ages 150
7.5 Comparisons between multiple trauma trajectories and depressive symptoms scores at various ages 151

8.1 Descriptives of the SMFQ between those with and without genetic data 167
8.2 Association between the depressive symptoms PRS and depressive symptoms at various across adolescence 169
8.3 Comparisons across ages between trajectories that have high and low PRS 171

Chapter 1

Introduction

1.1 Background and rationale

Depression is a major health concern, thought to affect approximately 300 million people around the world [1], and predicted to become the highest global burden of disease by 2030 [2]. Prevalence estimates vary, but lifetime risk of experiencing depression is thought to be as high as 18%, meaning that almost one in five individuals will go on to develop depression [3]. Depression is co-morbid with other mental health disorders such as generalised anxiety disorder and substance misuse [4, 5], and one of the leading risk factors for suicide [6]. Depression is also associated with social and educational impairments and reduced physiological wellbeing [7]. It is therefore important to examine the aetiology and nature of depression in order to prevent and reduce the impact of this illness.

Given that most psychiatric disorders such as depression are complex, it is not surprising that depression is often viewed as a dimensional phenotype [3]. For example, there is evidence that depression should be viewed on a continuum rather than just dichotomised [8, 9]. Studies have shown that increased depressive symptoms are a strong risk factor for a diagnosis of depression [10–12]. As such, it is possible to use a summarised score of depressive mood items as a proxy for investigating higher or lower depression symptomology. This is not to say that such measures are better than a clinical diagnosis of depression. Instead, these measures (which are usually the summary score of several items) can be administered quickly and are a cheap proxy for a face to face diagnosis which can be time consuming and expensive. Examining depression as a dimensional outcome using depressive symptoms has been useful for determining the presence of depression across research [12, 13]. However, in order to improve treatments and interventions for depression, it is important to identify and target rising symptoms at an early stage before they become more severe. The identification of early symptoms could therefore prevent

depression for occurring or reducing the likelihood of some of these negative social and psychological detriments.

One of the key stages of development where depressive symptoms often first arise is during adolescence [14, 15]. Thus, many researchers have targeted this stage of maturation in order to prevent depressive symptoms from escalating. Adolescence marks a period where depression will commonly onset, with almost 40% of individuals having their first episode before the age of 20 [3, 16]. Furthermore, 50% of individuals who experience depression before the age of 18 years old subsequently relapse later in life [17]. Adolescent depression is also a significant predictive of depression at later stage of life [18, 19], and a risk factor for other social and cognitive dysfunctions downstream [20]. Worryingly, recent evidence suggests prevalence of adolescent and young adulthood depression is increasing, with almost a fivefold increase in the number of young people reporting a mental health condition [21]. Therefore, research has focused on identifying the aetiology of adolescent depression to alleviate current and later depression.

1.2 Previous research, key limitations and potential solutions

Risk factors such as sex [22], maternal depression [23], childhood adversity [24], childhood bullying [25] and childhood psychopathology [26] have all been identified as potential risk factors for adolescent depression. Some of these are considered biological risk factors (sex), whilst others are considered environmental risk factors (adversity, bullying and psychopathology). Others still may be considered a mixture of both (maternal depression and psychopathology). Additionally, there is now the consensus that genetic factors also contribute to the onset and maintenance of depression [16, 27]. Much of the research on genetic influences of depression has been led by twin research [28]. However, there may be issues regarding generalisability with twin study designs. On the other hand, many non-twin studies have been unable to take genetic factors into account, likely because genetic data were not available (or in the cases where they were available, they were restricted to candidate genes which have been difficult to replicate). Recent advances in genomic research has meant that many longitudinal cohorts can now include alternative forms of genomic data such as measures of heritability and genetic liability scores (polygenic risk scores) to capture the genetic component of depression in an alternative framework to traditional twins research [29]. However, in many studies, the true longitudinal effect of these risk factors is not known as depression is only measured

on one occasion (i.e., at age 18). Therefore, the ability to fully understand the relationship between a risk factor and later depression is limited in studies that do not have multiple assessments of depression.

One way to explore the impact of risk factors on depression is to examine depression longitudinally using repeated measures that highlight the nature and changes of depression over time [30]. In the context of adolescent depression, it is important to examine when depression may be increasing or when it is at its highest as this could help tailor and improve interventions that may benefit wellbeing at a later stage of life. Likewise, if we can examine the course of depression and how and when it reaches this maximum (i.e., what are the antecedents for greater depression over time?), it may be possible to identify the key risk factors involved or preventative mechanisms that could help reduce depression over time. How depression changes over the course of development is therefore of great interest to researchers and clinicians alike. As figure 1.1 demonstrates, it is possible to use repeated assessments to go over and above traditional cross-sectional research methods to probe more information about the longitudinal nature of depression and its antecedents. Note that in the cross-sectional method, person 1 has greater symptoms. But using the repeated measures model, we can see that person 1 ends up with lower symptoms over time. The repeated measures model therefore gives more information.

Figure 1.1: Comparisons between cross sectional method (A) and repeated measures method (B). Note that in the cross-sectional method, person 1 has greater symptoms. But using the repeated measures model, we can see that person 1 ends up with lower symptoms over time. The repeated measures model therefore gives more information.

One of the most widely used methods for examining change in depression over time is growth curve modelling [30, 31]. Growth curve modelling can be achieved by using repeated measures of depressive symptoms from the same person over time (across multiple waves), which will highlight an individual's overall trajectory. This longitudinal approach has obvious advantages of some previous cross-sectional

approaches, as it possible to examine depression at multiple stages of development, rather than just one occasion.

Using this repeated measure approach, it is possible to highlight the course of depression for an individual, group of individuals or a population [32]. Several methods exist for deriving trajectories of depressive symptoms, which are discussed in greater detail in chapter 2. In brief, one key approach is to estimate trajectories for each individual and then capture the average trajectory across everyone – population averaged trajectory. A second key approach is to stratify individual trajectories into a limited number of groups of qualitatively distinct multiple-subpopulation trajectories that highlight hidden population subgroups - the latent class approach (referred to as the multiple trajectories approach from here onwards). Each approach can be combined with earlier risk factors to show how they can be associated with the varying trajectories.

Whilst growth curve modelling of depressive symptoms has been useful for examining the nature of adolescent depression, there are several key limitations of previous research, which I will state and aim to address in this thesis. These limitations are highlighted in greater detail in chapter 2.

Firstly, it is important to state that many studies do not have truly longitudinal data that captures the entirety of important periods of development. Depression will commonly onset during adolescence and it therefore important to track preceding and succeeding depression data to truly capture the nature of depression during this stage of development (i.e., from childhood all the way through to young adulthood). However, several studies only have data at certain key stages such as childhood to adolescence or focus on adolescence alone. This makes it difficult to conceptualise what the true pattern of longitudinal adolescent depression is and how a risk factor might affect that pattern. Tracking depression throughout this period with enough measures to capture any abrupt fluctuations in mood.

Secondly, previous research has often been limited to small or modest sample sizes, which can result in issues regarding generalisability. Large sample studies do exist [33, 34], but there are many studies that estimate complex growth curve models on smaller sample sizes that are not adequate and result in biased estimates, misinterpretations and contrasting conclusions [35, 36].

Thirdly, much of the previous work has been limited by the availability of existing data and methods. As discussed earlier, genetic factors are likely to play a key role in adolescent depression [16], yet the use of genetic methods in studies has been largely limited to twin studies. Incorporating both genetic and environmental[1]

[1]When I refer to genetic and environmental risk factors, that does not necessarily mean that all

risk factors into population studies is likely to further advance our understanding of the nature of adolescent depression.

Finally, there are also issues with the interpretation and translation of complex growth curve model findings into practice and policy. Using different methods to estimate growth curves of depressive symptoms (population averaged trajectories vs. multiple trajectories) can result in different interpretations of the same data. Likewise, more complicated models can produce estimates that are not easy to understand. For example, many trajectory estimates use higher order polynomials to describe changes over time. These estimates are sometimes referred to as linear, quadratic and cubic changes which highlight the nonlinearity of change over time and can give varying estimates that cannot be interpreted in isolation (i.e., the linear term goes up, the quadratic goes down and the cubic goes up). Translating these findings into more interpretable results (in conjunction with other research on predictions and diagnostic accuracy) could help pave the way for researchers, clinicians and policy makers develop better interventions and prevention strategies for depression.

1.3 Thesis aims and objectives

The aim of this thesis is to highlight how genetic and environmental factors contribute to trajectories of depressive symptoms. Specifically, this thesis will use a population cohort with multiple assessments of depression to achieve this main thesis aim and address many of the limitations of previous research which could help clarify the nature and aetiology of adolescent depressive symptoms.

Objectives

To achieve this overarching thesis aim, four research objectives are presented:

1. What are the varying patterns of longitudinal depressive symptoms across adolescence? To address this objective and build a platform for the rest of the thesis, I use two different growth curve methods (population averaged trajectory vs multiple trajectories approaches) to derive trajectories of depressive symptoms between childhood and young adulthood. This allows me to explore the utility of each approach and how different methods may produce varying or similar results and interpretations. This objective will build upon previous research that has been unable to examine a long enough duration of depression symptoms (i.e., transitions

these studies have both genetics and environmental data. I use the term genetic and environmental risk factors as an umbrella term to capture multiple risk factors including parental behaviour, bullying, genetic risk, childhood psychopathology, early life experiences and sex.

between childhood to adolescence, and adolescence to young adulthood). By examining a wide temporal window where symptoms change, it may be possible to better characterise the true nature of depressive symptoms across adolescence. Moreover, previous research has often been subject to smaller sample sizes which limit the generalisability of results to other populations and can be subject to bias. Creating growth curves for larger populations will go some way to alleviating those biases. Based upon previous research with limited and small data, I hypothesis that I will be able to detect a variety of heterogeneous subpopulation trajectories in the multiple trajectories approach (given the increase in power), and that population-averaged trajectories will differ by specific populations (i.e., different trajectories of males and females).

2. How are genetic and environmental risk factors differentially associated with varying trajectories of depressive symptoms? Here I utilise the two different growth curve methods to address this issue over several chapters. Firstly, I use the results from the popular multiple-subpopulation trajectories approach to examine how genetic and early environmental risk factors are differentially associated with varying longitudinal profiles of depressive symptoms in a multivariate fashion. Secondly, I run a series of analysis using the population-averaged trajectory approach to examine how these varying genetic and environmental risk factors are associated with overall depressive symptoms and changes in depressive symptoms over time. This allows me to highlight how each approach could be useful for examining the antecedents of trajectories of depressive symptoms. But importantly, it allows me to examine genetic and environmental risk factors in both a broad and specific manner (multivariate [multiple-subpopulation] and then univariate [population-averaged] approaches). This objective is key to this thesis as previous research has been limited by an inability to explore and compare both genetic and environmental risk factors within the same study, especially in longitudinal designs. Therefore, this objective expands upon previous work to include these risk factors. I hypothesised that both genetic and environmental risk factors will be associated with worse trajectories of depressive symptoms, and that certain risk factors (i.e., female sex and bullying) may yield stronger associations compared to other risk factors such as genetic risk for example.

3. Are there critical points in trajectories of depressive symptoms which tell us more about how and when depressive symptoms change across adolescence? I apply the results from the population-averaged trajectory approach to explore whether it is possible to identify critical or important points in trajectories of depressive symptoms such as when they are getting worse at the fastest rate or when they are at their maximum. This allows me to determine if the growth curve

modelling approach can be extended to help identify at risk individuals, before their depressive symptoms are at their worst. Previous research has yet to explore this notion of critical points, despite the fact that many growth curve studies suggest that there are sensitive periods where depressive symptoms may be increasing. I hypothesise that growth curve modelling can elucidate when depressive symptoms are getting worse and when they are at their worst, and these critical points might help infer more about the aetiology of adolescent depression.

4. Can the results from trajectory models be simplified to aid in the interpretation and translation of findings? For this last objective, I maximise the results from the three population averaged trajectory chapters to examine if there are alternative ways of presenting trajectory results from complex models. This allows me to explore if complex growth curve estimates can be better translated into more accessible results that could be useful downstream for policy makers and clinicians, and can help identify when a risk factor is likely to have its greatest effect on depressive symptoms.

It is important to clarify here that multiple chapters were used to address research objectives 2 and 4 (shown in table 1.1). This is done for several reasons. For research aim 2, I use multiple chapters to address this research aim as different growth curve methods have different utilities and could lend themselves to different interpretations. However, finding consistent results that have similar implications from both approaches would provide further evidence for addressing the research question and boosting the generalisability of both approaches. Likewise, one chapter (chapter 5) uses a multivariate analysis and in subsequent chapters (chapters 6, 7 and 8), I go into more detail to tease apart these associations. For research aim 4, multiple studies are used to provide context for the results (i.e., when translating complex estimates into a simpler interpretation, do the contexts of the results change when examining genetic risk compared to childhood trauma?).

1.4 Thesis structure

Much of the work from this thesis has been published or submitted for publication as five manuscripts in peer-reviewed journals (see below). Except for Chapter 2 (literature review), parts of chapter 3 (data and methods) and chapter 4 (the identification of varying trajectories), each of the thesis chapters presented form parts of publications or submissions, yet all these research chapters fall under the overarching theme of examining genetic and environmental contributions to trajectories of depressive symptoms. Here I produce a brief outline for what each chapter contains:

	Research Chapters				
Research Objectives	**4**	**5**	**6**	**7**	**8**
1. What are the varying patterns of longitudinal depressive symptoms across adolescence?	Y	-	-	-	-
2. How are genetic and environmental risk factors differentially associated with varying trajectories of depressive symptoms?	-	Y	Y	Y	Y
3. Are there critical points in trajectories of depressive symptoms which tell us more about how and when depression changes across adolescence?	-	-	Y	Y	Y
4. Can the results from trajectory models be simplified to aid in the interpretation and translation of findings?	-	-	Y	Y	Y

Table 1.1: Thesis research objectives. Note that in research objectives 2, 3 and 4, multiple research chapters can address each aim.

Chapter 2 presents a review of the current literature on trajectories of depressive symptoms across adolescence. This review was undertaken to summarise the previous literature, identify potential limitations in previous research and scope new avenues for research. In this review, I highlight these limitations and summarise previous methods for examining trajectories of depressive symptoms. I also summarise the findings from previous research on the nature and characteristics of trajectories of depressive symptoms across adolescence and identify the most robust risk factors that should be replicated in large samples with more assessments, and those risk factors that warrant more investigation. Stemming from this overview I identify the research gaps to form the basis of this thesis.

Chapter 3 introduces the data and describes the methods used in this thesis. The data come from the Avon Longitudinal Study of Parents and Children (ALSPAC), a longitudinal birth cohort study which has followed over 14,000 children and their families since the early 1990s. ALSPAC has an unparalleled richness of genetic and environmental data, as well as a number of repeated assessments of depression across development. In this chapter, I describe some of the issues with the ALSPAC study such as varying methods for data collection and attrition and introduce the key exposure and outcome variables used in this thesis. I then describe the two main analytical methods used to estimate trajectories of depressive symptoms in this thesis: the population averaged trajectory and multiple trajectories approaches.

In chapter 4, I apply these analytical methods to derive trajectories of depres-

sive symptoms in ALSPAC. This chapter uses the two main growth-curve methods identified in the literature review and chapter 3 to derive patterns of longitudinal depressive symptoms: firstly, I derive both the multiple-subpopulation trajectory and population-averaged trajectory approaches. I show here that each approach lends to varying and similar interpretations from the same data, however both approaches can be tailored to specific research questions where the utility of each approach is maximised. These trajectories are then used as the foundation for all subsequent chapters.

Chapter 5 uses the results from the multiple-subpopulation trajectories approach and limitations identified in the literature review to examine how both genetic and environmental risk factors may be differentially associated with varying trajectories. Using a multivariate approach to examine how multiple risk factors are associated with varying trajectories, I show here that it is also possible to differentiate trajectories that may be more reflective of either genetic or environmental risk factors, and possibly combinations of both. The key finding in this chapter is that being female, bullying and polygenic risk for depressive symptoms are all associated with higher trajectories, but can be differentiated to show specific associations. This chapter forms the basis for the following chapters which explore the association between these risk factors and trajectories of depressive symptoms in greater detail.

Chapter 6 then looks to replicate and extend one of the key findings from the literature review and previous chapter: that females are more likely to be associated with higher trajectories of depressive symptoms. Here I use the population-averaged trajectories approach from chapter 4 to estimate trajectories separately for males and females. I show that females are more likely to have higher trajectories of depressive symptoms across adolescence and young adulthood and that it is possible to identify critical points in these trajectories such as the age of peak velocity of depressive symptoms (i.e., the age where depressive symptoms are increasing most rapidly). I then show that females have an earlier age of peak velocity of depressive symptoms compared to males, and that this period may be useful for prevention and interventions.

Chapter 7 expands upon the previous chapters and findings from the literature review to examine the extent to which a key environmental risk factor, early childhood trauma is associated with varying trajectories of depressive symptoms. Using the population averaged trajectories approach established in chapter 4, I show that trajectories of depressive symptoms are higher for those exposed to childhood trauma compared to those who were not. I then show that this effect varies by the number of types of childhood traumas (such as bullying or abuse), with those having more types of childhood trauma being associated with the highest trajectory of depressive

symptoms. I present these results in an alternative framework (which simplifies the results from trajectory models) designed to aid in the interpretation and translation of these findings.

Chapter 8 also expands on the previous chapters and addresses a major limitation in the literature to explore how genetic risk for depressive symptoms (as measured by a polygenic risk score) might be associated with higher trajectories of depressive symptoms and how these results could be easily interpreted using an alternative results framework (established in the previous chapter). I show that greater genetic risk is associated with greater overall symptoms throughout adolescence, but also associated with a greater rate of change that begins to manifest in adolescence. I show that by using the methods derived in previous chapters, it is possible demonstrate that growth curve modelling has advantages over traditional cross-sectional methods, and this former approach could be useful for genomic methods.

Finally, in Chapter 9, I give some conclusions which provide a summary of all the research chapters and discuss how they address each of the thesis aims and their context within the literature. I show that all the chapters fall under the overarching theme within this thesis and demonstrate how having multiple chapters in support of a single research aim may strengthen the validity of those results. I also then highlight several limitations of the work conducted in this thesis and make several suggestions for future research.

1.5 List of publications and submissions

Chapter 3: Kwong, A. S. F. (2019). Examining the Longitudinal Nature of Depressive Symptoms in the Avon Longitudinal Study of Parents and Children (ALSPAC). Wellcome Open Res. 4: 126. doi.org/10.12688/wellcomeopenres.15395.1

Chapter 5: Kwong, A. S. F., Lopéz-Lopéz, J., Hammerton, G., Manley, D., Timpson, N. J., Leckie, G., Pearson, R. M. (2019). Genetic and Environmental Risk Factors Associated with Trajectories of Depressive Symptoms from Adolescence to Young Adulthood. JAMA Network Open. 2, doi:10.1001/jamanetworkopen.2019.6587

Chapter 6: Kwong, A. S. F., Manley, D., Timpson, N. J., Pearson, R. M., Heron, J., Sallis, H., Stergiakouli, E., Davis, O., Leckie, G. (2019). Identifying Critical Points of Trajectories of Depressive Symptoms from Childhood to Young Adulthood. Journal of Youth and Adolescence. 48, 815-827. doi.org/10.1007/s10964-018-0976-5

Chapter 7: Kwong, A. S. F., Maddalena, J. M., Croft, J., Heron, J., Leckie, G. (Under Review at Social Science and Medicine: Population Health). Early Child-

hood Trauma and Trajectories of Depressive Symptoms.

Chapter 8: Kwong, A. S. F., Morris, T. T., Pearson, R. M., Rice, F., Stergiakouli, E., Tilling, K., (Submitted to Psychological Medicine). Association Between Genetic Liability and Trajectories of Depressive Symptoms.

1.6 My contribution to this research

I conceived each chapter either jointly or in whole and led all the chapters in this thesis. I had sole access to the data used; cleaned, coded and prepared the data where necessary; conducted all the statistical analyses; interpreted the data either jointly or in whole; prepared first drafts of each chapter/manuscript; and had executive decision on all edits and changes to the final drafts of each chapter/manuscript.

Chapter 2

A Review on The Nature of Trajectories of Depressive Symptoms from Childhood to Young Adulthood: Methods, Predictors and Future Considerations

2.1 Introduction and chapter objectives

This chapter summarises the existing literature on trajectories of depressive symptoms across and beyond adolescence and identify any potential gaps in the literature that could be addressed throughout this thesis. As highlighted in the introduction, there are two popular methods for examining trajectories of depressive symptoms: the multiple-subpopulation approach and the population-averaged approach. This literature review synthesises and appraises both approaches before discussing the longitudinal nature of trajectories of depressive symptoms. I then go on to highlight several important risk factors for trajectories of depressive symptoms that have and haven't been explored in previous research. Finally, I give some considerations for future research that this thesis will aim to address.

2.2 Chapter abstract

Growth curve modelling has been used to derive trajectories of depressive symptoms across adolescence and young adulthood and previous research has demonstrated that these trajectories of depressive symptoms have a complex and multifactorial basis. Many social, biological and psychological risk factors have been identified to determine how and when they are having the greatest effects of adolescent depression in order to develop and improve interventions and treatments.

However, elevated levels of depressive symptoms first begin to manifest in adolescence, and this stage marks a period of substantial heterogeneity in depressive symptoms that can be difficult to measure. One of the biggest issues in growth curve modelling results from how this heterogeneity is modelled. One popular method is to stratify individuals into multiple-subpopulation trajectories (or latent classes). An alternative approach is to model the population-averaged trajectory. This choice of modelling comes down to whether the researcher believes the heterogeneity should be discrete or continuous.

In this chapter, I give an overview of these two popular methods for deriving trajectories of depressive symptoms. I then synthesise previous research on trajectories of depressive symptoms across the transition between childhood and young adulthood to provide a comprehensive understanding of the nature, shape and characteristics of these trajectories. I then highlight the key risk factors used in previous studies, before giving some considerations for future research which could enhance the understanding of the nature of trajectories of depressive symptoms and treatment and prevention of depression.

2.3 Introduction

Growth curve modelling has been used to help explore the aetiology and nature adolescent depression [37]. Taken from repeat measures of an individual, growth curve modelling is an efficient method for examining the antecedents of depressive symptoms, change in depressive symptoms over time and later downstream consequences [32, 38, 39]. Growth curve modelling has advantages over cross-sectional paradigms as it is possible to estimate how depressive symptoms change over time and not just observe depressive symptoms at one occasion. Likewise, through the use of repeated assessments, it is also possible to get a better representation of an individual's true depressive symptoms score as measurement error may be present during cross-sectional methods, and this error may be reduced when considered lon-

gitudinally. The most common application of growth curve modelling is to derive trajectories, in this case trajectories of depressive symptoms. From here onwards, the term trajectories will be used interchangeably with growth curve modelling, unless otherwise specified.

2.3.1 Trajectories of depressive symptoms from childhood to young Adulthood

The use of trajectories for examining depressive symptoms from childhood to young adulthood has increased in recent years. This has likely coincided with advancements in new methods such as growth mixture modelling [40, 41], and the availability of new repeated data [32]. Using this trajectories approach, many social, biological and psychological risk factors such as parental behaviour, social class, ethnicity and early child psychopathology have been identified [35, 42, 43]. Additionally, this methodology has become more important as trajectories can be useful tools for identifying pathways to later psychopathology and other impairments [43]. This importance is highlighted by a recent systematic review on trajectories of depressive symptoms across the life course in 2016 [32] and two systematic reviews published in 2017 on trajectories of depressive symptoms in young people [30, 31].

2.3.2 Existing limitations and considerations of trajectories of depressive symptoms research

Although examining trajectories of depressive symptoms in young individuals has enhanced our understanding of the mechanisms underlying risk factors for depressive symptoms, there are still many limitations and considerations observed across previous studies that are of note to this thesis. First, trajectories of depressive symptoms across adolescence are heterogeneous and these trajectories can be classified into discrete or continuous heterogeneity, depending on the methodology. This has a profound impact on the interpretation of the results as some studies group trajectories into multiple-subpopulation trajectories (i.e., group-based trajectories or latent classes – discrete heterogeneity), whilst others use population-averaged trajectories (hierarchical linear models or multilevel growth-curve models – continuous heterogeneity). This means it is sometimes difficult to compare trajectories across multiple studies. Secondly, some studies only examine trajectories of depressive symptoms at a certain period (e.g., adolescence), whilst others capture data across the transition between several developmental periods (e.g., childhood to adolescence or adolescence to adulthood). If only a snapshot of the data is captured, then it is

not possible to infer more about the nature of trajectories of depressive symptoms and inconsistent patterns can emerge. Finally, many studies have been limited by the availability of existing data and have been unable to explore key risk factors for trajectories of depressive symptoms such as genetic or familiar risk. This means that there are many avenues for research which are left incomplete and are worth addressing to help further explore the aetiology of adolescent depressive symptoms.

2.3.3 The current review

The purpose of this review is to highlight previous research and shed light on some of the limitations and existing considerations in growth curve modelling research across adolescence and young adulthood. For simplicity, I use the phrase 'childhood to young adulthood' to describe these studies, even though many of these studies will only cover certain ages or transitions. I also use the term "higher" trajectories to describe trajectories that have more severe or less favourable patterns of depressive symptoms – thus higher trajectories are perceived to be negative throughout this chapter (note, I also use this term throughout the thesis). In this review, I first give an overview of two popular methods for deriving trajectories of depressive symptoms and then critically appraise each approach. Secondly, I then synthesise previous research on trajectories of depressive symptoms across childhood and young adulthood to provide a comprehensive understanding of the nature, shape and characteristics of these trajectories. I then highlight the key risk factors identified in previous studies and identify risk factors which require further research. Finally, I give some considerations for future research which I will then address in the remainder of this thesis.

2.4 Statistical methods for examining trajectories of depressive symptoms

2.4.1 Methodological variation

There are several ways to model trajectories of depressive symptoms which may impact on the interpretation of these trajectories. As shown in figure 2.1., one primary method is to stratify repeat measures of depressive symptoms into multiple-subpopulation trajectories (the group-based method – discrete heterogeneity) which all have qualitatively distinct trajectories that represent a group of individuals over time for example, those with consistently low symptoms (stable low) or those with

symptoms that rise throughout childhood (childhood rising) [41, 44–46]. An individual then has a probability (and an associated degree of uncertainty) of belonging to one of these subpopulation trajectories based upon their responses [40, 47]. A risk factor (e.g., sex or ethnicity) may then be added into the model to increase/decrease the odds of an individual belonging to a certain trajectory, that is conditional of the model. The number of subpopulation trajectories identified tends to range between 3-5, but as many as 6 have been estimated in previous studies [30–32]. This method is described as the multiple-subpopulation trajectories approach or multiple trajectories approach from here onwards. An alternative approach is to estimate individual trajectories of each person that can then form an overall population trajectory [48, 49]. These population trajectories are often referred to as population-averaged growth-curve models or latent curve models and display the trajectories in a continuous heterogeneity manner [49, 50]. These trajectories are composed of an intercept and slope, which quantifies the rate of change (or uses these parameters to describe the the growth-curve). A risk factor (e.g., sex or ethnicity) is then associated with the trajectory to investigate its impact on the intercept and rate of change [30].

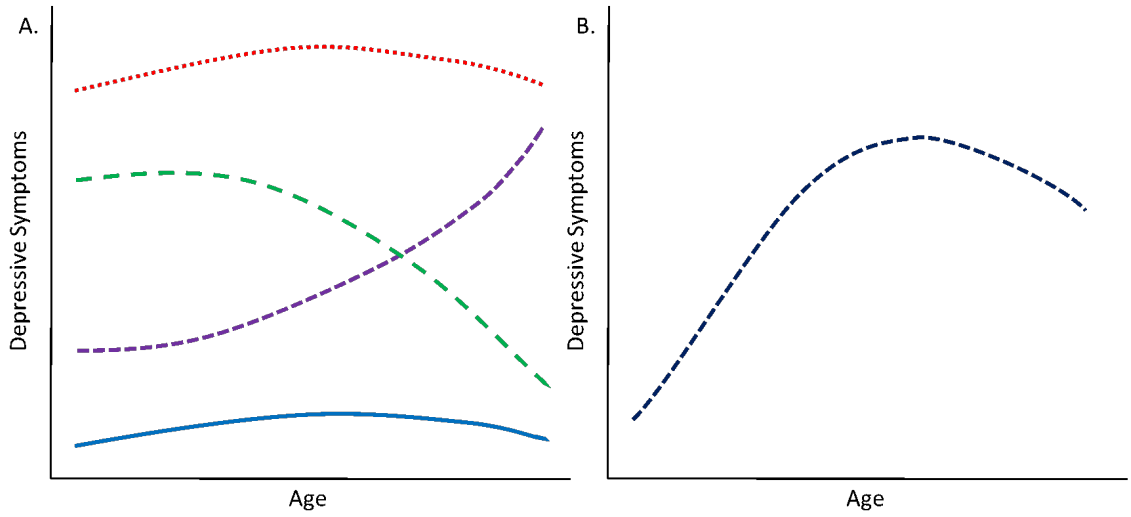


Figure 2.1: Comparison between multiple-subpopulation approaches such as Growth Mixture Modelling (GMM) or Latent Class Growth Analysis (LCGA) where trajectories could be 'low', 'increasing', 'decreasing' and 'high' (A.) and population-averaged trajectory approaches such as Hierarchical Linear Models (HLM) or Multilevel Growth-Curve Models (MLM) where the trajectory could be the average depressive symptoms score in the population (B.).

It is important to highlight that while both methods aim to quantify the nature and change of trajectories of depressive symptoms, they both vary in their approach to answering growth curve research due to how they each deal with the heterogeneity of individual level trajectories. Consequently, the degree to which it is possible to compare across studies using the two varying methodologies depends on the research

questions involved. In the following section, I discuss the underlying approach for each method and the potential advantages and disadvantages in relation to exploring trajectories of depressive symptoms between childhood and young adulthood.

2.4.2 Multiple-subpopulation trajectories

Multiple-subpopulation trajectories have greatly enhanced our understanding about the heterogeneity of depressive symptoms within populations [32]. There are various forms of the multiple-subpopulation approach, however the overarching principle of these multiple-subpopulation approaches is that they predict the posterior probability that an individual belongs to a certain subpopulation trajectory. Latent Class Growth Analysis (LCGA) or Semi-parametric group-based models (SPGBM) classify individuals into qualitatively distinct subpopulation trajectories in which there is often assumed to be no within-group variance (i.e., everyone within this trajectory follows the same pattern) [40, 45, 46]. Multinomial logistic regression (or some alternative e.g., basic logistic regression or analysis of variance [ANOVA]) is then used to associate a risk-factor with a specific trajectory (against a comparison or baseline trajectory – often a low or high trajectory) which can shed light on which risk factors are associated with higher/lower trajectories [35, 37, 42]. However, as depressive symptoms are heterogeneous and can fluctuate greatly over time [51], it is unlikely that everyone within a subpopulation trajectory will follow the same pattern and such models may be inadequate for measuring heterogeneous depressive symptoms.

To circumvent this, Growth Mixture Models (GMM) and General Growth Mixture Models (GGMM) have been used as an alternative approach to modelling multiple-subpopulation trajectories [40, 41, 44]. GMM is a simple extension to LCGA/SPGBM that allows variance to occur within-group subpopulation trajectories (i.e., individual trajectories may all be classified into one subpopulation trajectory but may have different patterns within that overarching trajectory). With GMM, it is possible to explore the impact of a predictor on multiple trajectories and then which trajectory may impact on a later outcome, all within a one-step model [52]. A biased adjusted three step model that incorporates the uncertainty regarding trajectory classification can also be used [53]. Like, LCGA/SPGBM, associations between a risk factor and a varying trajectory can be established with through multinomial logistic regression or some alternative for GMM approaches. GMM and GGMM have been increasingly popular for estimating trajectories of depressive symptoms during the transition across childhood through young adulthood with many studies using this approach and finding consistent evidence of multiple

subpopulation trajectories of depressive symptoms across various populations [32].

Advantages. There are many advantages for the multiple-subpopulation approach. For instance, a priori knowledge about the nature and shape of trajectories is not required as the number of trajectories identified are formally tested using some model fit criterion (usually through the smallest Bayesian information criterion [BIC], highest entropy or likelihood ratio test [these are discussed in greater length in the methods and data chapter]) [54]. This can also lead to a hypothesis free approach that discovers potentially meaningful latent classes that might have been overlooked in other forms of growth modelling [47]. Additionally, problems with random variation are minimised in multiple-subpopulation models as variance is stratified into subgroup populations [55]. This also means there are fewer problems with over/underfitting of the model. Multiple-subpopulation models can also include covariates in the original model allowing for a degree of flexibility in model fit [52]. Similarly, it is easy to explore associations between multiple risk factors and trajectories in a multivariate approach, which means it is a popular approach when considering multipe risk factors at one time. Finally, these studies are easy to conduct in many software packages such as R, SAS or Mplus and can show clear and easy to interpret associations between risk factors and specific trajectories [40].

Disadvantages. However, there are several disadvantages to the this approach which are important to highlight. The first is that the identification of subpopulation trajectories are based upon posterior probabilities and that every individual trajectory belongs to every class, just some have a higher degree of certainty as to which class they should belong to [56]. However, this can be minimised in a bias adjusted three step model which considers this uncertainty and reduces this potential bias. A more pressing concern is the possibility that some subpopulation trajectories identified from multiple-subpopulation models don't exist [57]. This may be especially true with small sample sizes when trajectories are made from few individuals or when the data are not normally distributed and non-linear. Likewise, it may not be possible to form adequate trajectories when there are few measurements, and 4 or 5 measurements are often preferable to ensure the adequate identification of trajectories [58]. The shape of trajectories can also change with the addition of covariates – especially when trajectories are built in multiple stages (i.e., stage one identifies the trajectories, stage two adds in covariates, stage 3 adds a distal outcome – and each have missing data). If multiple studies are using the same data source, but examining including different covariates into the initial model, there is the possibility that different trajectories will be estimated [53]. Additionally, when the data are missing at random (MAR), there may be problems in recovering the correct number of subpopulation trajectories and errors in the probability of belonging to a specific

subpopulation if the individuals missing from the data are missing for a specific reason [58]. For example, if an individual has two low scoring depressive symptoms measurements than misses the following two measurements due to depression (missing not at random [MNAR]), the model would specify that the individual had a low trajectory of depressive symptoms which is not the case. Finally, multiple-subpopulation models may not adequately capture severe fluctuations in the data. Depressive symptoms can rapidly change from each occasion and subpopulations may not properly model these fluctuations.

2.4.3 Population-averaged trajectories

An alternative approach is to estimate trajectories of depressive symptoms through the population-averaged approaches such hierarchical linear models (HLM) [48], multilevel growth-curve models (MLM) [59] or latent curve models (LCM) [60]. Here, each individual trajectory is measured, and then a single population trajectory can be identified that is the average of all these individual trajectories. This trajectory is characterised by two factors: an intercept (starting point) and a slope (rate of change [more advanced rates of change will be discussed in the data and methods chapter]). Risk factors can then be included into the model to examine associations between an intercept and/or slope. Like multiple-subpopulation trajectories, there are variations in how trajectories of depressive symptoms can be modelled. For example, HLM and MLM assume that repeat measures of depressive symptoms are nested within individuals and growth curves can be derived to form individual level and subsequent population-averaged trajectories [49]. There is a degree of flexibility in how population trajectories are modelled as the slope (i.e., rate of change) can be estimated using various functions of time (usually polynomials). This is discussed in greater detail in chapters 3 and 4. A similar approach is to estimate latent curve modes via a structural equation modelling framework (SEM) [60]. Here, the trajectory is characterised by unobserved latent growth factors such as the intercept and slope. The additional benefits of using the SEM approach is that specific depression items, pathways and mediation models can be estimated in a growth curve framework. The population-averaged approach can also be estimated in many statistical packages such as Stata, SAS, R, Mplus and SPSS.

Advantages. There are several advantages of the population-averaged trajectory approach. The first is that this approach gives a clear understanding about the nature of a trajectory within a given population [49]. Model fit can be tested by BIC or deviance to examine the best fit for the trajectory [61]), and derived trajectories can be displayed next to descriptive data to visually examine model fit. The second

advantage is that it is easy to explore rates of change within the population-averaged approach. For example, it is possible to associate a risk factor with the rate of change to investigate if depression is getting worse faster or slower. Consequently, it could then be possible to examine if a risk group (e.g., males vs females) has a steeper trajectory compared to another and if there is worse at a given time. Thirdly, many HLM and MLM methods are more friendly to longitudinal studies as they allow for a varying number of measurements per person, inconsistent spacing between measurements and account for missing data [48], whereas methods like GMM may have convergence issues with these factors.

Disadvantages. However, there are several disadvantages of the population-averaged approach. The first is that population-averaged trajectories only describe the average course of depressive symptoms within a population. Critics of this approach argue that a single trajectory is not sufficient to model the heterogeneity of depressive symptoms within the population and just estimating the means of the population may not be enough to fully explain the nature of depressive symptoms [62]. The second is that choosing how to model the slope (i.e., the polynomials) is more subjective then the multiple-subpopulation approach as researchers do require some a priori knowledge about the underlying nature before choosing a model that fits the data. Whilst BIC and deviance can be used to assess model fit, there is more subjectivity with the population-averaged approach. Thirdly, unlike the multiple-subpopulation approach, it is much harder to conduct and interpret multivariate models, especially when there are continuous and categorical risk factors. Finally, like the multiple-subpopulation approach, there is also the issue of missing data. HLM and MLM models tend to assume that data are MAR which can lead to biased estimates if the data are MNAR.

2.4.4 Methods summary

In summary, there are merits and pitfalls to both approaches that must be considered during study design (see table 2.1 for an overview). Ultimately, whilst the multiple-subpopulation and population-averaged approaches vary in how they classify the heterogeneity of depressive symptoms (discrete vs continuous heterogeneity), it is possible that both methods could be used to draw inferences about the nature of trajectories of depressive symptoms and their aetiology. The preferred approach for examining trajectories of depressive symptoms will still depend on the overarching research question and in some scenarios, one approach may be more beneficial than the other. However, the two methods could be used to complement one another if results are potentially harmonisable. The greatest obstacle is comparing the

overall shape between multiple-subpopulation trajectories to population-averaged trajectories (as there often between 3-5 trajectories that take various shapes vs one population-averaged trajectory). But if a pattern emerges whereby a risk factor uniformly associates with "higher" subpopulation trajectories and is also associated with a higher population-averaged trajectory, then it may be possible to utilise both approaches rather than use any single approach alone. This thesis will use both methods to further explore this possibility and examine if using information from both approaches can lead to stronger inferences regarding the genetic and environmental contributions to trajectories of depressive symptoms. This will be further considered in the conclusions chapter.

	Multiple-subpopulation trajectories	Population-averaged trajectories
Summary:	Known as LCGA, SPGBM, GMM and GGMM Multiple subpopulation trajectories Predicted odds of membership into each class Odds of risk-factor being associated with each class Often conducted in Mplus or SAS	Known as HLM, MLM, LGA One trajectory per population Coefficients for intercept and slope Often conducted in Stata, SAS, R
Advantages:	No a priori knowledge about the classes Minimised random variation Fewer problems with model fit Model fit tested by BIC or entropy	Can examine rate of change of a population Flexible time function (i.e polynomials) Varying measurements and inconsistent spacing Easy to test model fit
Disadvantages:	Membership into class based upon probabilities Risk of bias in one-step models Potentially non-existent classes Problems with few measurements Problems if data are not missing at random	Population trajectory may not be sufficient More subjective modelling of trajectories Polynomials may perform poorly at tails Problems if data are not missing at random

Table 2.1: Summary of various trajectory methods. LCGA: Latent class growth analysis, SPGBM: Semi-parametric growth-based modelling, GMM: Growth mixture modelling, GGMM: General growth mixture modelling, HLM: Hierarchical linear models, MLM: Multilevel growth-curve models, LGA: Latent growth analysis, BIC: Bayesian information criterion.

2.5 Previous findings on trajectories of depressive symptoms between childhood and young adulthood

2.5.1 Number of trajectories

The number of trajectories identified in previous studies will vary depending on the methodology. Multiple-subpopulation approaches will typically identify multiple trajectories (at least 3). However, population-averaged trajectories may only identify one (depending on the number and nature of the risk-factors), especially if the associated risk factor(s) is a continuous outcome such as a score. In the following section, I refer to multiple-subpopulation modelling approaches when discussing the number of trajectories that have previously been identified in the trajectories of depressive symptoms between childhood and young adulthood literature (unless otherwise stated). This is because this approach is more popular and always results in multiple trajectories, whereas the population-averaged approach will only tend to identify the population trajectory.

Most studies report between 3 or 4 distinct subpopulation trajectories, although up to 6 have been found in some studies [63–65]. Additionally, some studies also fit separate models for sex, so that males and females can have a different number of trajectories [56, 66, 67]. The number of trajectories identified will also depend on varying sample sizes over different age ranges and duration of follow up/number of measurements. Conceptually, larger sample sizes may have greater power which results in more trajectories identified. However, this is not always the case. Heath and Camarena used data on 268 American children assessed between the ages of 11-14 years, over 3 years (6 waves) and derived 6 subpopulation trajectories of depressive symptoms [65]. However, similar studies with roughly comparable sizes, ages and follow ups have observed 3 or 4 trajectories [62, 68]. Likewise, other studies with larger follow ups and waves [38, 69, 70], have identified fewer trajectories than studies with smaller follow ups and less waves of data [62, 71, 72]. Of note, when the sample size surpasses 3000 individuals, there appears to be less variation in the number of classes identified with most studies identifying at least 4 trajectories of depressive symptoms [34, 37, 63, 73–79]. This is likely a result of more date resulting in increased power to detected any meaningful differences between the subpopulation trajectories. The inconsistency surrounding the number of trajectories identified in previous studies is therefore likely be partially dependent on sample size, duration of follow up and the number of measurements and sample size.

2.5.2 Characteristics of trajectories

The description of these trajectories tends to vary, but in most studies, there are common trajectories that emerge regardless of sample size, cohort or measure. As shown in figure 2.1., the most commonly identified trajectories are often labelled 'low', 'stable-low' or 'absence of symptoms' for individuals with low or no depressive symptoms [34–37, 62, 63, 68, 73, 75, 80], and 'high' or 'persistent high' for individuals with constantly high depressive symptoms [43, 71, 72, 81–84]. In between these, there are intermediary trajectories that have been identified as: 'increasing', 'decreasing', 'moderate', 'transient' and 'adolescent-onset', all of which appear in various forms across studies [34, 37, 62, 69, 71, 73, 75, 85, 86]. These intermediary trajectories vary more than the "low" or "high" trajectories and are likely dependent on when depressive symptoms were assessed, follow-up duration and sample size. Nevertheless, these intermediary trajectories are more challenging groups to quantify given the heterogeneity of depressive symptoms. However, not all studies will simply have these "low", "high" and intermediary trajectories. Some studies have identified trajectories based upon their onset such as 'low', 'moderate early', 'severe early' and 'late' [35], or 'adolescent onset' and 'high childhood' [34, 87], whilst others have found that both high and low trajectories change over time: 'increasing' and 'decreasing' [38], and 'low and declining', 'moderate and stable' and 'high increasing' [69]. These trajectories are potentially more interesting as these describe the nature of a trajectory, but also qualitatively describe when it is beginning to occur (i.e., an onset during adolescence or limited to childhood). Such trajectories may be more informative within developmental research as they provide more information on an individual's trajectory than a simple "increasing" or "decreasing" label.

The number of individuals belonging to these varying trajectories also tends to differ. In a systematic review of 20 studies, Shore and colleagues found that about 67% (range: 24-93%) of individuals across these studies belonged to some low trajectory group [31]. Individuals belonging to a 'high' trajectory contributed 3% (range: 0-25%), whilst 17% (range: 0-76%), 4% (range: 0-22%) and 8% (range: 0-23%) belonged to a 'moderate', 'increasing' or 'decreasing' trajectory respectively. In a separate systematic review on 47 studies, Schubert and colleagues suggested that between 60-80% of individuals fall into a lower trajectory, whilst between 5-12% of individuals belong to higher trajectories. Schubert and colleagues also suggested that intermediary trajectories that vary by shape and numbers may be dependent on specific population characteristics and sample size [30].

2.5.3 Shapes of trajectories

The shapes of the trajectories also differ for both multiple-subpopulation and population-averaged approaches. In many multiple-subpopulation studies, intermediary trajectories take linear and non-linear patterns where they increase/decrease across time and then level out, continue increasing/decreasing or eventually plateau. In multiple-subpopulation approaches, there may be several trajectories that follow a cross-diagonal shape like the pattern shown in figure 2.1 (A) [35, 36, 75, 77, 86]. Some studies also have multiple opposing non-linear trajectories that cross one another. For instance, Repetto and colleagues observed high and low trajectories that surrounded two increasing and decreasing trajectories in adolescence [83]. Costello and colleagues observed two trajectories that were stable (no depressed mood and low) and two cross-diagonal trajectories with one starting high and decreasing (early high) and one rising through adolescence and into young adulthood (late escalating) [37]. Studies that show non-linear trajectories imply that depressive symptoms are affected by severity (low, moderate or high), chronicity (childhood limited or high persistent) and stability (stable, increasing or decreasing) [32].

Population-averaged trajectories also show severity, chronicity and stability and highlight how trajectories of depressive symptoms within the population are heterogeneous and not stable. Studies have shown linear [88–92], and nonlinear trajectories [18, 33, 93–96]. Nonlinear trajectories of depressive symptoms research are typically explored with quadratic growth. Edwards et al. (2014) showed that depressive symptoms between male and female populations followed different shapes, with male trajectories having a more rising inverse quadratic shape (a convex shape), whilst females had a more traditional quadratic shape that declined towards adulthood (a concave shape). Quadratic trajectories of depressive symptoms have been used to model growth curves in multiple studies [97–100]. For more complex trajectories, cubic growth has also been explored when quadratic growth cannot adequately capture the depressive symptoms [101, 102]. The fact that both multiple-subpopulation trajectory and population-averaged trajectory approaches show varying degrees of severity, chronicity and stability provides evidence that the two methods can be used to complement one another. In the data and methods section and the first research chapter, I will discuss this notion of linearity and non-linearity in greater detail.

2.5.4 Nature of Trajectories

Given that several trajectories are often identified in multiple-subpopulation approaches and this obviously contrasts the number identified by population-averaged

approaches, the observable nature of depressive symptoms from childhood to young adulthood is not entirely clear. Research has suggested that trajectories of depressive symptoms tend to increase from late childhood but peak during or towards the end of adolescence, around the ages of 15-17 [18, 30, 97–99, 101, 103]. Other studies suggest this peak occurs earlier or later, but may not have data that precedes or succeeds adolescence, making it harder to investigate whether these effects are universal and can lead to contrasting patterns and varying inferences [42, 62, 81, 93, 96, 100].The nature of trajectories of depressive symptoms from late childhood to young adulthood will be better understood from studies that use data from a wide enough time period as these studies can highlight the dynamic patterns, shapes and characteristics of trajectories which could be translated into treatment and prevention for depression.

The nature of these trajectories of depressive symptoms from childhood to young adulthood is typified by the number of trajectories identified, their characteristics and their shapes. These are then based upon stability, chronicity and severity. Evidence suggests that both multiple-subpopulation and population-averaged trajectories are not only heterogeneous (and vary between approaches) but are also dynamic across this stage of development and can be difficult to assess.

2.5.5 Risk factors for trajectories of depressive symptoms between childhood and young adulthood

This next section provides an overview of the risk factors associated with trajectories of depressive symptoms across childhood to young adulthood. It is important to state here that when I discuss risk factors, I am referring to predictors of these trajectories and not causal mechanisms. That is to say that when exploring associations between risk factors and trajectories, the association is correlational and not presumed to be causal. Many of these risk factors could be causal or on the causal pathway, yet the current study designs do not allow for causal estimations to be made.

Sex differences. The most consistent finding in the literature is that females are at greater risk of higher trajectories of depressive symptoms from childhood to young adulthood [1]. This is consistent with a wealth of cross sectional and longitudinal research showing that females have a greater preponderance to depressive symptoms compared to males [3, 16, 22]. In multiple-subpopulation methods, females are more likely to belong to be associated with the more severe and chronic trajectories of

[1]Whilst this a biological risk factor, there is so much research on it that it warrants its own section.

depressive symptoms. For instance, females were more likely to be associated with the 'high and persistent' trajectories compared to males [42, 64, 71, 103]. In other studies, being female often shows a stronger association with "higher" and intermediary trajectories [34, 43, 56, 79, 83]. However, there are some instances where sex is not associated with "higher" trajectories [104]. Instead, Olino and colleagues found that being female was associated with greater odds of belonging to the 'late onset', 'increasing' and 'initially high' trajectories, but not the 'persistent high trajectory'. Similar results were observed by Costello and colleagues who showed stronger associations for females belonging to the 'early high', rather than 'late escalating' trajectories [37]. Such findings imply that being female may not automatically be associated with "higher: trajectories. Instead, more nuanced sex mechanisms may exert themselves at different times which may have downstream effects of depressive symptoms (i.e., around puberty or transition into adolescence) [105]. An example of this is highlighted by Lee and colleagues who showed that females were more likely to belong to a higher trajectory in adolescence but not in young adulthood [106].

Similar results are also observed for population-averaged trajectories where females are often associated with a higher intercept and steeper slope [18, 93, 97, 99]. Additional research has also shown that the rate of change between sexes also varies. Chen and colleagues observed that females had initially greater depressive symptoms, but these symptoms declined faster than their male counterparts [89]. Similar effects have also been observed in other studies [99]. However, other research has found no evidence of sex differences regarding rates of change [102, 107] or opposite effects with increased depressive symptoms across time for males in comparison to females [108]. The extent to which sex is associated with rates of change warrants more research to clarify this issue as mixed findings could be a result of the time period assessed (i.e., adolescence or young adulthood). Additionally, there is some evidence of sex interactions with other risk factors such as social-economic status/stressful life events [97], dating status [99], parental behaviour [34] and self-esteem [102], which in turn can have more negative effects on female trajectories of depressive symptoms.

Ethnicity. Another strong risk factor for less favourable trajectories of depressive symptoms from childhood to young adulthood is ethnicity. There is evidence that ethnic minorities are at risk of higher trajectories of depressive symptoms and this is observed across multiple methods and populations [30]. In one study, being of African, Latino or Asian descent was associated with the 'early high' trajectory [37]. However, these ethnicities were not associated with the 'late escalating' trajectory, implying that association between ethnicity and greater depressive symptoms is stronger in early adolescence, rather than later on in development. Adkins and col-

leagues observed higher trajectories of depressive symptoms for African, Asian and Hispanic descendants, but only Asian descendants showed a faster decrease across time – implying there are differential effects between ethnicities [97]. Similar results have also shown an association between Asian descendants and higher trajectories of depressive symptoms, but that symptoms begin to decrease and match White individuals after 15 years of age [89]. Finally, higher ethnic discrimination is associated with higher trajectories of depressive symptoms [100], indicating additional social influences other than being an ethnic minority may contribute to worse depressive symptoms.

Socioeconomic status and poverty. The association between socioeconomic status (SES) / poverty and trajectories of depressive symptoms is less clear than other risk factors. Several studies have demonstrated that low SES is associated with higher trajectories of depressive symptoms from childhood to young adulthood [97]. Adkins and colleagues observed strong sex interactions where females in low SES were associated with greater depressive symptoms. Other studies have also shown that lower SES is associated with a greater likelihood of being in "higher" trajectories of depressive symptoms [37, 103] and similar findings have shown that lower poverty is associated the lowest depressive symptoms trajectory [77]. However, in other research, this association is not replicated. For instance, several studies have found no association between lower SES and less favourable trajectories [34, 35]. It is unclear why SES is associated with trajectories of depressive symptoms in some studies, but not others. One reason may be SES is a proxy for other measures of the "physical" environment (i.e., residency, mobility or earnings), and studies may require more nuanced analyses to further explore this association.

Psychological risk factors. Many psychological risk factors have been associated with trajectories of depressive symptoms. Hankin showed that negative cognitive styles mediated the relationship between females and higher trajectories of depressive symptoms [109]. Additionally, Hankin also found that rumination and interactions between rumination and stress was also strongly associated with higher trajectories of depressive symptoms. In a similar study, negative affectivity, negative cognitive styles and rumination were all associated with membership into "higher" trajectories of depressive symptoms [38]. Likewise, negative cognitive styles was associated with both the 'high-declining' and 'high-persistent' trajectories of depressive symptoms [110]. Other psychological risk factors such as lower human agency (belief in one's self) have also been associated with higher trajectories of depressive symptoms and may mediate the relationship between poorer communities and greater depressive symptoms [111]. Similarly, inter-personal dependency and loneliness were associated with membership into several "higher" trajectories of depressive symptoms, whilst

a higher coping score was associated with a stable-low trajectory [43]. Lower self-concept has also been associated with a higher trajectory across adolescence [103].

Other psychological risk factors such as poorer temperament [35] and greater pessimism and avoidance [70] have also been associated with higher trajectories of depressive symptoms. Likewise, Weeks and collagues found that greater conduct and hyperactivity scores in childhood were associated with the the 'adolescent onset', 'high childhood', 'high stable' and 'moderate stable' trajectories, whilst difficult temperament was associated with all but the 'adolescent onset' trajectory [34]. Externalizing, and avoidant behaviour in early development have also been associated with membership into "higher" trajectories of depressive symptoms [112]. Additionally, risk factors like childhood anxiety, peer rejection, social competency and attentional problems are all associated with increased "higher" trajectories of depressive symptoms throughout adolescence [80]. Anxiety was also associated with greater depressive symptoms during childhood to late adolescence in another study, although depressive symptoms decreased across time [92]. Low self-control has also been associated with both 'moderate' and 'high' trajectories of depressive symptoms [82]. In a separate study, lower self-esteem was associated with steeper trajectories of depressive symptoms, although this effect was only prominent in females [102]. Similar effects of low self-esteem being associated with higher trajectories of depressive symptoms have also been shown [83]. However, what is not clear in many of these studies is how reciprocal these effects are (i.e., how low self-esteem may reinforce greater depressive symptoms and vice versa).

Parental depression has been strongly associated with some of the higher subpopulation trajectories of depressive symptoms [34, 36, 43, 74, 104, 106]. However, what is less clear is how the timing of parental depression (i.e., prenatal vs postnatal) and the effect of each parents plays a role in trajectories of depressive symptoms as these studies did not discriminate between these timings. In other studies, parental depression has not been associated with any of the "higher" trajectories [80, 112] suggesting this intergenerational pathway may be complex and require more sensitive analysis to tease apart.

Social risk factors. Many of the strongest risk factors for higher trajectories of depressive symptoms from childhood to young adulthood have social underpinnings. For example, witnessing partner violence as a child was associated with higher trajectories of depressive symptoms across adolescence and later in life [113]. These effects were worse for females and for children without social support. Similarly, abuse suffered before the age of 18 was strongly associated with the 'persistent', 'increasing' and 'initially high' trajectories, but not the 'later onset' trajectory of depressive symptoms [104], suggesting that the timing of abuse may be important

and have more immediate consequences rather than long term. Stressful life events (or negative life events) such as emotional or physical neglect have also been associated with "higher" trajectories of depressive symptoms across multiple studies [36, 43, 88, 98]. There is also evidence that stressful life events increase female trajectories of depressive symptoms, but not males [97, 107], however, the opposite effect has also been observed in another study [74]. Research has shown that the number of stressful life events may play an important role as more than two stressful life events in early life were strongly associated with membership into the "higher" trajectories of depressive symptoms [34]. The timing of stressful life events may also play a role as stressful life during adolescence have also been shown to be associated with a "higher" subpopulation trajectory [112]. However, there has also been no association observed between stressful life events and trajectory membership in several studies [80, 86], indicating that the timing and context of these stressful life events is likely to play an important role in this association – it may not be enough to simply classify different stressful experiences together. Instead it may be beneficial to explore the number of stressful life events over a period of time – to examine time specific outcomes, or specific types of events such as emotional neglect or physical abuse.

Other social factors such as lower parental educational attainment and a disruptive family structure have also been associated with "higher" trajectories [34, 37, 77, 114]. For example, children not part of a 2-parent family structure were more likely to be associated with a higher subpopulation trajectory of depressive symptoms [37]. Likewise, family adversity was associated with membership into the 'consistently high' trajectory of depressive symptoms [62], whilst family dysfunction has been associated with 'high childhood', 'high stable' and 'moderate stable' trajectories [34]. Ge and colleagues also observed that children from divorced families had higher trajectories of depressive symptoms, and that this effect was worse for females [98]. As yet, no studies have examined the association between the timing of parental separation and trajectories of depressive symptoms, as this could play an important role. Worse relationships with parents have been shown to a risk factor for higher trajectories of depressive symptoms [34, 62, 85, 86, 107]. For example, Weeks and colleagues found hostile and punitive parenting were both associated with the 'high childhood' trajectory. Parental substance abuse such as excessive smoking and drinking have also been associated with higher trajectories of depressive symptoms, independently of childhood/adolescent substance misuse [34, 43]. However, this association is likely to be complex and hard to disentangle as parental drinking at ages 4 and 12 has not been associated with trajectories of depressive symptoms in a separate study [115].

Substance use has been shown to be a strong risk factor for higher trajectories of depressive symptoms. Marmorstein found reciprocal associations for higher depressive symptoms and alcohol problems, but that greater alcohol consumption was associated with much higher trajectories of depressive symptoms [5]. These effects varied by sex with females showing stronger associations and a slower decrease in depressive symptoms compared to males. In other studies, similar effects of alcohol consumption have been observed [79, 108, 116, 117]. Smoking has also been associated with higher trajectories of depressive symptoms [118], and Wickrama and Wickrama showed that excessive smoking was associated with the higher trajectories [78]. Similar effects were shown also shown by Rodriguez and colleagues who demonstrated that baseline smoking was associated with increased depressive symptoms over time [84]. Overall, general substance abuse has been associated with the 'high stable' trajectory compared to the 'low-decreasing' trajectory [43], suggesting there may be long term effects of substance use that may not recover over time. Substance use was also associated with the 'early high' trajectory [37], implying that such effects may also have immediate consequences. These findings are not surprising given that mood and substance abuse disorders are highly co-morbid [5], and may imply that mood and substance use disorders share a common pathway.

Other social risk factors such as negative dating experiences have also been identified as risk factors for higher trajectories of depressive symptoms [99, 106], although evidence suggests that this effect may only be present in young adulthood [106]. Similarly, poorer quality relationships with friends and peers have been associated with much higher trajectories of depressive symptoms [62, 70, 81]. Marshal and colleagues found that sexual minority youths were at a much greater risk of higher trajectories of depressive symptoms, with this association strongest for females [95]. Similar findings were also observed by Needham who showed that consistent gay/lesbian/bi-sexual attraction was associated with higher trajectories of depressive symptoms across adolescence [119].

Biological risk factors. Several biological risk factors have also been associated with higher trajectories of depressive symptoms. Ferro and colleagues showed that individuals with chronic illness were associated with higher trajectories of depressive symptoms, which decreased at a slower rate across adolescence and young adulthood [101]. Similar effects were also observed by Weeks and colleagues who showed that chronic illness was associated with the 'high childhood' trajectory, but when interacted with sex, females were more likely to belong to the 'adolescent onset' trajectory – implying there may be differential effects for sexes with regards to chronic illness [34].

One important risk factor for higher trajectories of depressive symptoms is

pubertal status. Previous research has shown that early maturation is associated with a higher trajectory of depressive symptoms [93]. In the same study, this effect was amplified for females. Additionally, females with recent stressful life events were more vulnerable to higher trajectories of depressive symptoms. Other findings have demonstrated that early pubertal timing was also associated with the 'early high' trajectory, although this effect did not differ by sex [38]. In another study, both early and late puberty was associated with higher trajectories of depressive symptoms, yet the effect diminished over time [99]. Interestingly, Natsuaki and colleagues observed that females with early/late maturation who also experienced negative effects of dating were at a greater risk of higher trajectories of depressive symptoms.

Other studies have suggested mothers who experience stressful life events during pregnancy may have offspring with higher trajectories of depressive symptoms via in utero expsoure. Kingsbury and colleagues found that the number of stressful life events in pregnancy was associated with the 'consistently high' trajectory [75], implying that stressful events may impact on development in utero, which has downstream consequences. The role of genetics has also been explored in several studies. Lubke and colleagues assessed the twin heritability of trajectories of depressive symptoms and found that heritability was higher for trajectories in comparison to cross sectional measurements of depressive symptoms – implying that 1) trajectories may better methods for assessing genetic effects compared to cross sectional methods and 2) that change in depressive symptoms over time may have a genetic component [120]. Genetic variation has also been identified as a potential risk factor for varying trajectories of depressive symptoms. In one study, two candidate dopamine receptor variants (D2D2 and DRD4) were associated with higher trajectories of depressive symptoms [94]. In another study, carriers of the dopamine receptor D4 5-repeat allele were associated with trajectories of depressive symptoms that started higher, yet decreased more rapidly until early adulthood where they began to rise again [33]. In the same study, carriers of the monoamine oxidase A 3.5R allele also had a higher trajectory of depressive symptoms compared to carriers of other monoamine oxidase A alleles. However, these findings are from candidate gene studies which are notorious for false positives and consistently lack replication across studies [121]. There is now the consensus that there is no one "gene" for depression or depressive symptoms, instead the genetic epidemiology of depression is likely to be complex and comprised of multiple genetic variants, each contributing small effects [9, 122, 123]. These multiple genetic variants can be tallied to create a polygenic risk score that measures an individual's genetic liability to depression [29]. To date, only one study has examined polygenic risk score in relation to trajectories of depressive symptoms and found that a greater risk score (i.e., greater genetic liability to depression) was associated with an "adolescent-onset" trajectory – im-

plying that genetic liability to greater depressive symptoms may begin to manifest in adolescence [87].

Risk factors summary. The studies described here demonstrate that multiple social, biological and psychological risk factors are all associated with higher trajectories of depressive symptoms. Many of these risk factors occur early in life, implying that they have long term effects on depressive symptoms but provide a potential opportunity to intervene at an early stage of development. Alternatively, it may be useful for services and policy makers to be aware who are at the greatest risk of higher trajectories of depressive symptoms that may need to more routinely followed. There is evidence that sex may play a role in mediating or moderating these trajectories and future research should control for sex or use sex interactions to explore these mechanisms further. Likewise, there may be multiple environment interactions that facilitate higher trajectories of depressive symptoms such as SES. There are several risk factors such as genetic liability which have shown promise in early studies but require more research. Crucially, the findings from many of these studies show comparable results between multiple-subpopulation trajectory and population-averaged trajectory approaches. This suggests that whilst both methods handle heterogeneous trajectories differently, the findings can be somewhat compared with regards to identifying risk factors for higher trajectories of depressive symptoms.

2.6 Limitations in previous studies and considerations for future research

2.6.1 Small duration of follow-up and lack of waves of data collection

There has been a plethora of research on adolescent trajectories of depressive symptoms, yet there are still many limitations in previous research that this thesis will look to address. The first is that a major limitation in previous studies regards the duration of follow-up and the number of waves of data collection. In several studies, depressive symptoms are measured over two-year [81, 86, 113] or three-year periods [62, 65, 71], often around adolescence. Depressive symptoms are likely to be greatest during adolescence between the ages of 15-17 [30], yet consistent evidence for this, and the identification of the exact ages has not been fully established. This makes it difficult to determine when depressive symptoms are at their worst, which would be important to identify regarding treatment and support. This paucity in

research arises from a lack of studies that measure depressive symptoms across a wide enough period. Studies that measure depressive symptoms over a small duration of follow-up are unable to infer more about the preceding and succeeding nature of trajectories of depressive symptoms, only that trajectories may be higher/lower during that age range. Depressive symptoms are dynamic and can change rapidly across a short period of time [51]. Therefore, it is necessary to have studies with frequent repeated assessments of depressive symptoms over multiple stages of development to fully capture any nuanced changes and achieve a more holistic approach to examining the nature of trajectories of depressive symptoms.

2.6.2 Size matters

Many of the studies exploring trajectories of depressive symptoms from childhood to young adulthood have used small sample sizes which may not be applicable to the general population or result in bias. In several studies, sample sizes are fewer than 150 individuals [86, 100, 113], so the extent to which we can generalise these findings to the wider population may be limited. Other studies have used larger sample sizes ranging between 200 and 400 individuals with varying methods, risk factors and cohorts [18, 35, 36, 81, 91]. As mentioned earlier, studies using multiple-subpopulation trajectories may be less applicable for smaller studies as they categorise people into qualitatively distinct subpopulation trajectories with potentially small classes that are not representative of the population or are statistical artefacts that result from this model. These concerns have previously been raised as smaller studies using multiple-subpopulation methods may have a higher risk of bias then population-averaged trajectories [58]. However, the counter to this is that depression prevalence rates within the population are generally similar to some of these higher subpopulation trajectories, and so low numbers of individuals are expected. Similarly, studies using larger sample sizes have also demonstrated comparable group sizes to smaller studies. Nevertheless, we must be cautious about the claims made in studies using small sample sizes and larger longitudinal cohorts would be preferred to minimise some of the biases in previous research.

2.6.3 Future research

Multiple-subpopulation trajectories and population-averaged trajectories have demonstrated that multiple risk factors are associated with trajectories of depressive symptoms from childhood to young adulthood. However, there are avenues for future research which could improve our understanding of the nature of these trajecto-

ries and translation into prevention and treatment for depression. This review has highlighted many limitations in previous research such as difficulties in harmonising varying growth curve approaches (and so the overall nature of trajectories across development is not clear) and a lack of investigation in some risk factors (i.e., genetic and some environmental risk factors, and combinations of the two). However, there are several additional limitations that thesis also aims to address.

One research gap is that whilst previous research has explored the nature of trajectories and risk factors for these trajectories, very little is known about critical points for trajectories (i.e., when are depressive symptoms at their highest?; When are they getting worse or better?; When is a risk factor having the greatest effect on these trajectories?). Identifying critical points along trajectories could help researchers, services and policy makers determine what ages or stages are the best time to intervene to reduce or potentially prevent greater symptoms from occurring. Likewise, it may be important to identify when depressive symptoms are increasing the fastest as there is the potential to intervene at these ages to stop depressive symptoms persisting or getting more severe. Previous research has already called for more research to explore critical periods outside of the trajectories literature [124] and research in other fields has begun to derive critical periods for other forms of childhood growth such as height [125]. However, such research has yet to be extended for trajectories of depressive symptoms, and this is a limitation of previous research that this thesis will explore. In particular, identifying when a risk factor is having its greatest effect on trajectories of depressive symptoms, and comparing this to other ages could be of great use to clinicians and policy makers as it provides an age that could be targetable for a host of interventions and treatments.

A second gap in the literature, but a more general limitation of previous research is how these results can be used to guide policy and clinical treatment. There is evidence that trajectories derived from repeated measures models may be better than cross-sectional research [120], but there may be issues in how the results from growth curve studies are interpreted. One concern is that it hard to compare between multiple-subpopulation and population-averaged trajectories (as discussed earlier). A second is that population-averaged trajectories are likely to be non-linear across adolescence and require advanced modelling to appropriately capture these trajectories. This can result in complex estimates are that are hard to interpret and communicate to non-statistical audiences, all of which prevents the translation from research to clinical practise. Presenting complex results in a more interpretable manner will not only address these concerns but help guide future research.

2.7 Conclusions

This chapter has highlighted that trajectories of depressive symptoms from childhood to young adulthood are multifactorial and associated with a number of risk factors, with several risk factors warranting more investigation. Trajectories of depressive symptoms are estimated using varying growth-curve methodologies but can be affected by variation in cohorts, duration of follow up and the timing of assessments. It may be possible to use both multiple-subpopulation and population-averaged approaches to complement one another as they often highlight similar findings and combining these two approaches could pave the way for better treatment and interventions for depression. The nature of these trajectories is complex and still not fully understood given the variability found in many previous studies. This thesis will look to address these concerns by primarily examining how genetic and environmental contributions are associated with trajectories of depressive symptoms. To do this, I will further probe the nature of depressive symptoms across this period by utilising both growth-curve approaches. I will look to replicate and expand upon the risk factors identified earlier in this review and further the existing literature by examining the notion of critical periods and providing more interpretable results from complex estimates in my models. This thesis will also make use of a large sample size and use depressive symptoms data with a long duration of follow that will help quantify the nature of depressive symptoms from childhood to young adulthood and build upon the existing literature.

2.8 Chapter summary

This chapter has summarised the previous literature on trajectories of depressive symptoms and highlighted several key points and limitations that can be used to build the platform for this thesis. The first is that multiple growth curve methods can be used to explore trajectories of depressive symptoms and that using both methods may be more beneficial than one single approach alone. The second is that there are several genetic and environmental risk factors for trajectories of depressive symptoms that have been robustly identified in previous research, but there are several that require more investigation such as genetic liability and childhood adversity. Third is that previous research can be expanded to identify the notion of critical points such as when symptoms are getting worse and when a risk factor is having its greatest effect. Finally, the results from varying growth-curve models can be complex and could be more easily translated into simpler estimates that are more readily interpretable. This thesis will aim to address these limitations through the four

research objectives stated in the introduction. First, I will derive trajectories of depressive symptoms using the two approaches described here - this will build a platform for the rest of the thesis to explore genetic and environmental contributions. Immediately after, I will use the more common approach of establishing multiple-subpopulation trajectories in order to explore the association between genetic and environmental risk factors and trajectories of depressive symptoms in a multivariate approach. The following 3 chapters (6, 7 and 8) will then expand upon these findings to disentangle some of the complex genetic and environmental associations using the population-averaged approach. In the conclusions chapter, I will sum up how these various approaches have helped answer the overarching research question and how these findings relate to the existing literature described within this chapter. More immediately, in the next chapter I will go on to introduce the data and methods used throughout this thesis.

Chapter 3

Data and Methods

3.1 Chapter introduction

This chapter provides the reader with an introduction to the data and methods used throughout the thesis. Firstly, I outline the source of the data and how it was collected. Next, I introduce the depressive symptoms data which are the focal point of this thesis. Here I discuss how depressive symptoms are measured and the descriptive statistics and longitudinal patterns of the data. I then highlight some considerations for the depressive symptoms data such as attrition and bias. Finally, I give a brief introduction to the statistical methods used in this thesis: population averaged trajectories (created using multilevel growth-curve models) and multiple trajectories (growth mixture models).

Part of this chapter was published as a Data Note in Wellcome Open Research as below. This chapter therefore has elements of that publication.

Kwong, A. S. F. (2019). Examining the Longitudinal Nature of Depressive Symptoms in the Avon Longitudinal Study of Parents and Children (ALSPAC). Wellcome Open Res. 4: 126. doi.org/10.12688/wellcomeopenres.15395.1

3.2 Data source

The data used in this thesis is from the Avon Longitudinal Study of Parents and Children (ALSPAC), an ongoing population-based study in the South-West of England designed to examine the effects of a number of factors on health and development surrounding pregnancy (see figure 3.1). Full details regarding the study are described in the cohort profiles [126, 127] . ALSPAC initially recruited pregnant mothers with an estimated delivery date between April 1991 and December 1992. The initial co-

hort consisted of 14,541 pregnancies, which resulted in 14,092 live births with 13,988 children still alive one year later. When the children were approximately seven years old, ALSPAC attempted to recruit eligible children who were not recruited between April 1991 and December 1992. This resulted in an increased sample of 15,247 pregnancies with 14,775 live births, of which 14,701 children still alive one year later [128].

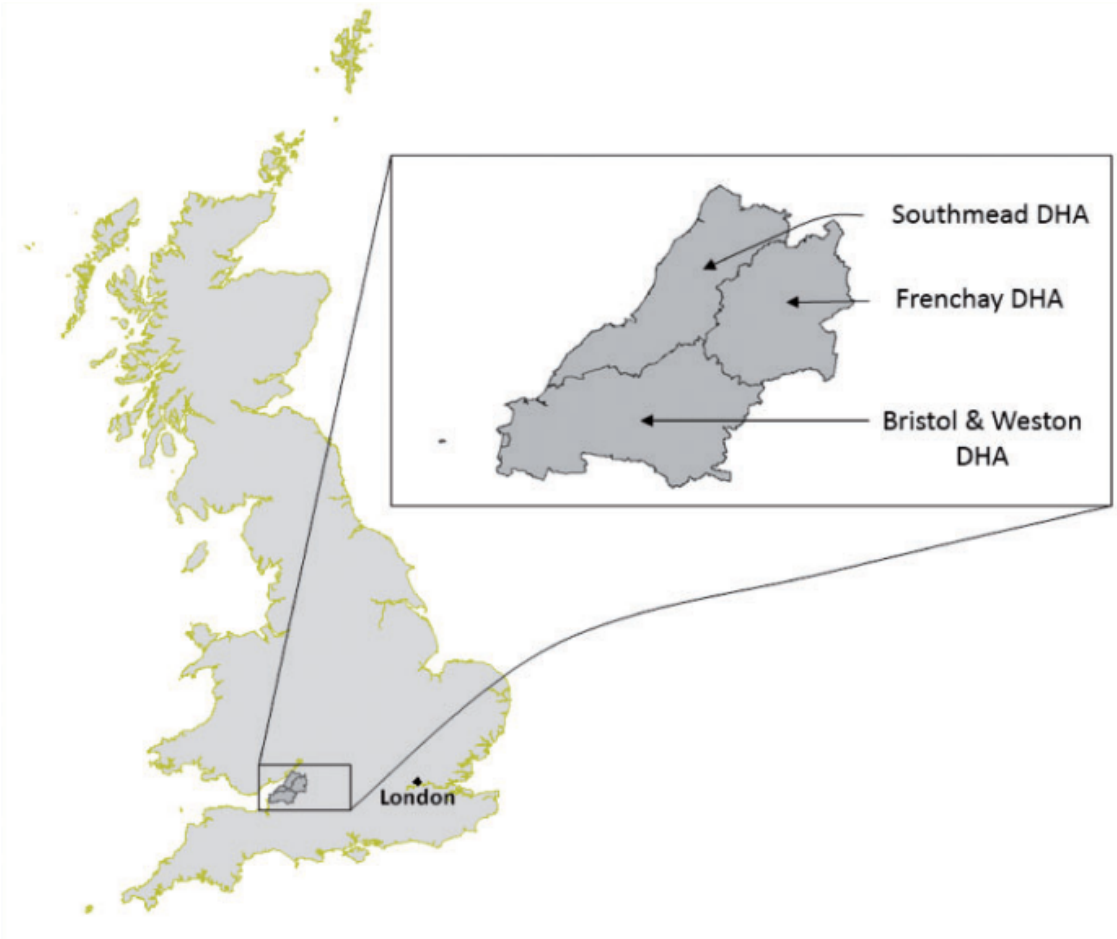


Figure 3.1: ALSPAC recruitment areas [126]. DHA: District Health Area. Figure reprinted with permission.

As ALSPAC is a multiple generational study currently spanning currently just under 30 years, the data come from multiple respondents in a variety of methods. For example, data has been collected through questionnaires, clinic assessments and data linkages to medical, obstetric and educational records. For questionnaires, these have been completed by the mother, her partner, children and their teachers in both self-report format and parent/teacher reported format. At clinic assessments, biological samples (hair, urine, biomarkers and blood) and physical and psychological assessments have been measured giving anthropometric data (height, weight and lung function) as well as genetic and epigenetic data. This thesis mainly focuses on the self-reported data from the children/young-people but maximises

the use of the biological samples (for genetics) and parent reported data (for exploring risk factors). I will discuss this in more detail in subsequent chapters. Further information about the data in ALSPAC is available on the study website (www.bris.ac.uk/alspac), which also contains a fully searchable data dictionary (www.bris.ac.uk/alspac/researchers/data-access/data-dictionary). ALSPAC has its own Law and Ethics Committee that reviews and manages all projects that use ALSPAC data. Furthermore, projects that collect new data are approved by the Local Research Ethics Committees. This thesis had approval from the Law and Ethics Committee.

ALSPAC is largely representative of the UK population, yet it has been noted that children included within the study were more educated at age 16 compared to the national average, more likely to come from homeowner backgrounds and more likely to be of Caucasian descent [126]. Additionally, analysis by Boyd and colleagues found that children who had participated in a questionnaire and a clinic assessment around age 17 had greater educational attainment compared to those who had not participated at these assessments or those who were lost to attrition. Therefore, it is possible to argue that individuals enrolled in ALSPAC may differ from the national average and this may not lead to generalisable results. This is discussed in greater detail in the overall limitations section in the final chapter and in several research chapters.

3.2.1 Depressive symptoms

ALSPAC is one of the few longitudinal cohorts that has repeated assessments of self-reported depressive symptoms. Furthermore, ALSPAC has measured depressive symptoms more frequently across adolescent development than many other studies, making it an invaluable tool for exploring the nature of depressive symptoms. The literature review highlighted that many studies do not have repeated measures data will enough duration of follow up, or enough measures to capture any nuanced changes throughout adolescence. In ALSPAC, depressive symptoms are measured using the short mood and feelings questionnaire (SMFQ). In this part of the thesis, I describe the SMFQ and the nature of depressive symptoms in ALSPAC.

The short mood and feelings questionnaire (SMFQ)

The SMFQ is a 13-item questionnaire that measures the presence of depressive symptoms in the last two weeks [129]. The SMFQ has been used in clinical and general populations for examining depressive symptoms [14, 15]. Table 3.1 shows the list of questions used in the SMFQ, that were also used in ALSPAC. For each of the 13-item questions, the response can be "not true" (scored 0), "sometimes" (scored

1) and "true" (scored 2). Each question is scored between 0-2 and the resulting summary score of all the items can range between 0-26, with higher scores being more indicative of greater depressive symptoms. Previous research has shown that the SMFQ is predictive of adolescent clinical depression in ALSPAC [13], and research has used the SMFQ for exploring the potential risk factors for higher depressive symptoms [75, 87], and the later consequences of greater depressive symptoms [108, 130].

Question number	List of questions used
1	I felt miserable or unhappy
2	I didn't enjoy anything at all
3	I felt so tired I just sat around and did nothing
4	I was very restless
5	I felt I was no good anymore
6	I cried a lot
7	I found it hard to think properly or concentrate
8	I hated myself
9	I was a bad person
10	I felt lonely
11	I thought nobody really loved me
12	I thought I could never be as good as others
13	I did everything wrong

Table 3.1: List of short mood and feelings questions (SMFQ). For each question, the responses are: not true (scored 0), sometimes (scored 1) and true (scored 2). The total scores are then added up to give a score ranging between 0 and 26 where higher scores indicate higher depressive symptoms.

SMFQ within ALSPAC

The SMFQ was measured on nine occasions between the ages of 10 and 24 in ALSPAC. At each of these occasions, the SMFQ was self-completed by the child/young person. The SMFQ was administered in ALSPAC via postal/email questionnaire or at research clinics depending on the wave. Table 3.2 shows how each occasion was collected. The SMFQ in ALSPAC was not collected at regular age intervals and table 3.2 shows the mean age of participants at each assessment. There is no obvious pattern for time between assessments but the longest period between assessments was between the ages of 18.6 and 21.95. The shortest period was between the ages of 17.84 and 18.65.

Characteristics of the SMFQ in ALSPAC

As shown in table 3.2, the sample size of the SMFQ sample varies in ALSPAC,

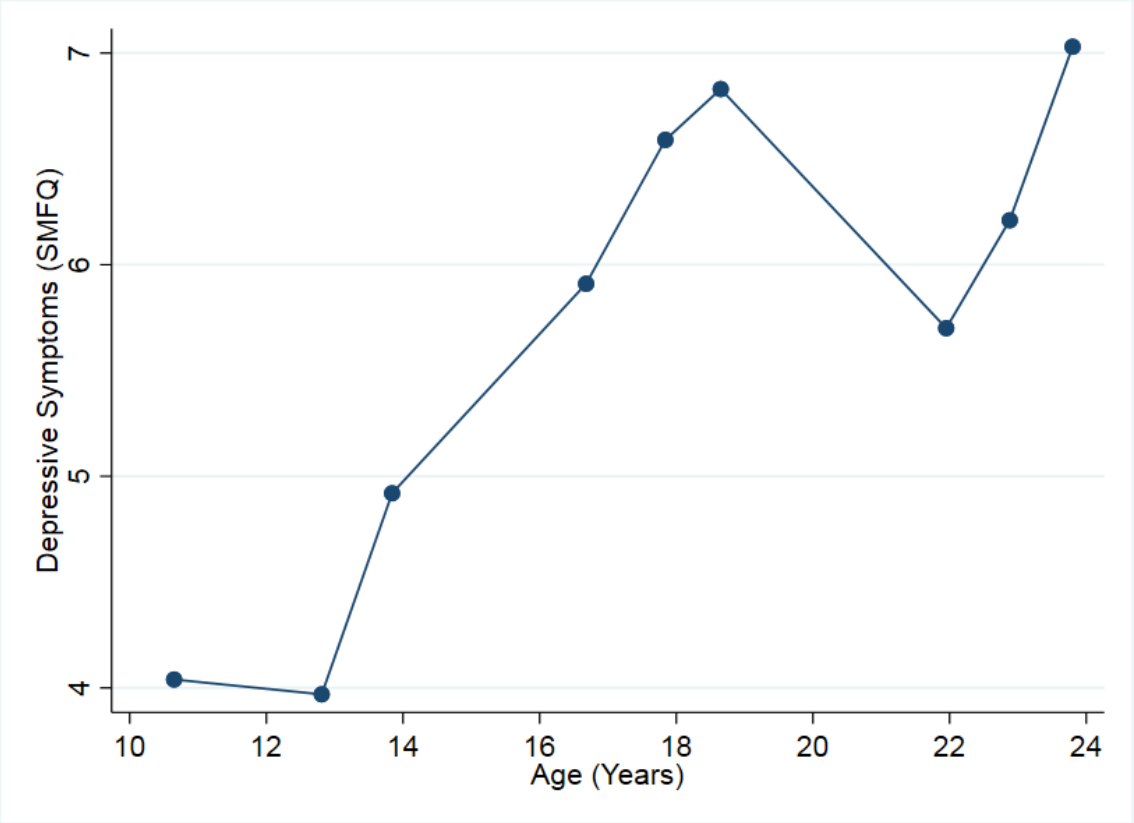


Figure 3.2: The mean depressive symptoms scores of each occasion, as measured by the short mood and feelings (SMFQ) questionnaire in ALSPAC.

with a maximum of 7,364 individuals at the first occasion (age 10.65), compared to the minimum sample of 3,305 at the seventh occasion (age 21.95). Thus, ALSPAC and the SMFQ in particular is subject to attrition, which I will discuss later in this chapter and again in the overall limitations section in the conclusions chapter. The profile of attrition can be seen in table 3.2. Additionally, one of the thesis research aims was to identify the nature of depressive symptoms across adolescence and beyond. Here I give a brief description of the depressive symptoms data in ALSPAC but will use more advanced statistical methods to quantify the nature of depressive symptoms in the next chapter. Table 3.2 and figure 3.2 both highlight how the SMFQ changes over time with all the data available. In chapter 6, I discuss sex differences in depressive symptoms but for the overall sample, individuals had initially low levels of depressive symptoms in late childhood. Scores then tended to increase until the age of 18. From here, depressive symptoms began to decline until the age of 22, where symptoms then began to rise again to greater levels than previously observed at age 18. There was more heterogeneity around the data towards the later stages of data collection with higher standard deviations observed, implying there was more variability towards the later stages of adolescence and early adulthood. Figure 3.3 shows histograms for the nine occasions of the SMFQ.

Occasion	Mean Age	Sample Size	SMFQ Mean	SMFQ SD	SMFQ Median	SMFQ IQR	α	SMFQ Source
1	10.65	7,364	4.04	3.51	3	5	0.797	Clinic
2	12.81	6,716	3.97	3.86	3	4	0.842	Clinic
3	13.84	6,019	4.92	4.49	4	5	0.865	Clinic
4	16.68	4,997	5.91	5.64	4	6	0.908	Questionnaire
5	17.84	4,497	6.59	5.25	5	7	0.897	Clinic
6	18.65	3,335	6.83	5.93	5	8	0.906	Questionnaire
7	21.95	3,305	5.7	5.58	4	6	0.915	Questionnaire
8	22.88	3,856	6.21	5.55	5	7	0.906	Questionnaire
9	23.8	3,915	7.03	6.06	5	8	0.913	Questionnaire

Table 3.2: Descriptive statistics and reliability of the SMFQ within ALSPAC. α was measured using Cronbach's alpha.

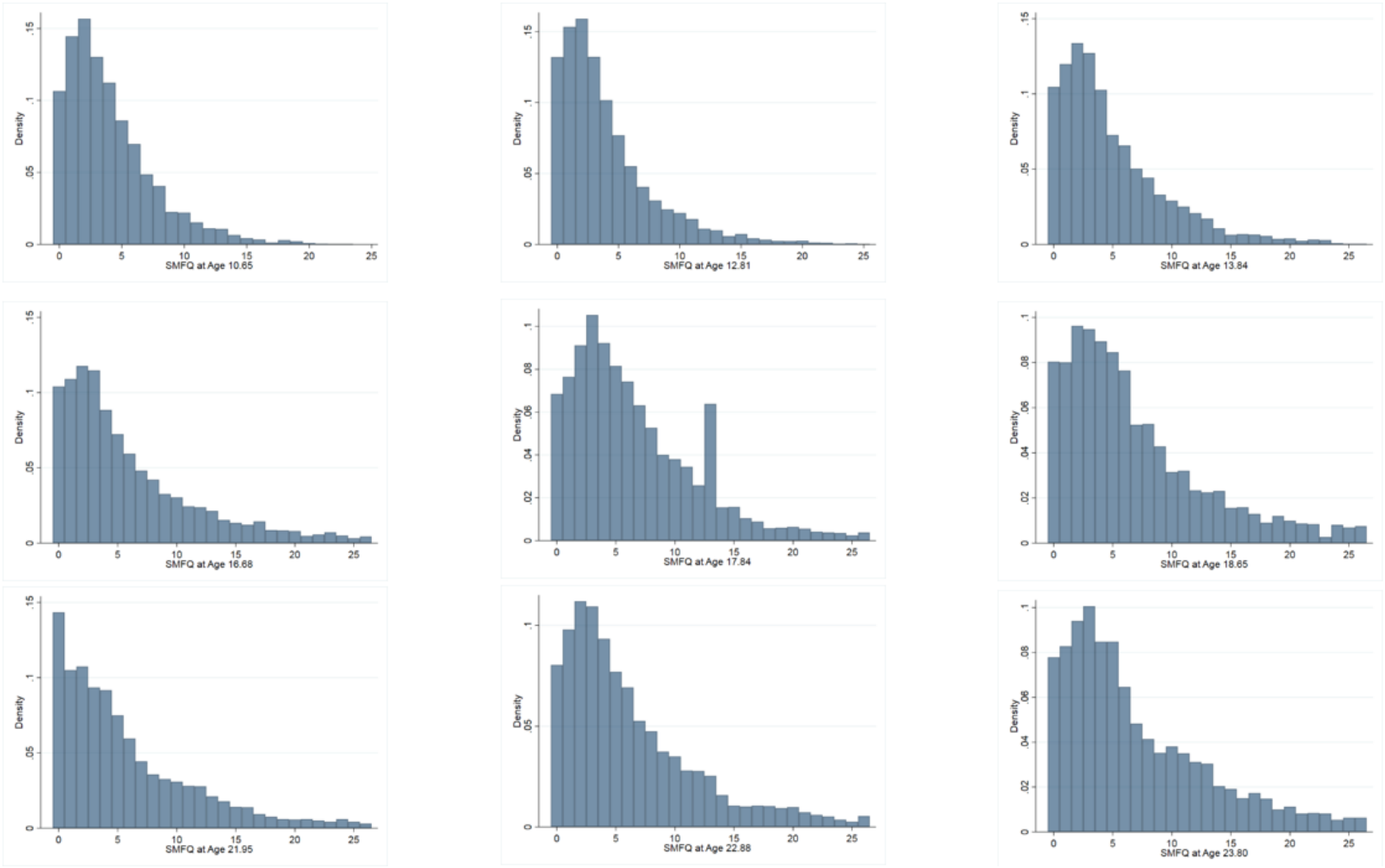


Figure 3.3: Histograms for the short mood and feelings questionnaires (SMFQ) at each of the nine occasions in ALSPAC.

Validity and utility of the SMFQ

Within ALSPAC, the SMFQ has good internal reliability as assessed by Chronbach's alpha [1]. Table 3.2 shows that the reliability was lowest on the first occasion (0.797) and highest on the seventh occasion (0.915), which suggests that earlier assessments may not have been as well understood as the later assessments. There were strong correlations observed between each of the assessments (Ps $< .0001$). As table 3.3 shows, there was a pattern where occasions measured more closely together had higher correlations (i.e., ages 10.65 and 12.81, compared to the correlations between ages 22.88 and 23.8), and these were particularly strong towards the last three assessments ($r > .569$), which could imply that depressive symptoms are more similar at later stages of development and vary at different stages (i.e., depressive symptoms mean different things to at different ages – yet at the later stages they mean the same thing). The strong correlation between all the assessments indicated that the SMFQ is a valid tool for examining depressive symptoms over time within ALSPAC.

[1] Even though there was good reliability at each occasion, that does not mean that the SMFQ is measuring the same construct at each occasion. In the conclusions chapter, I give a discussion about what this might mean for the thesis and how it may limit some of the results.

	Age 10.65	**Age 12.81**	**Age 13.84**	**Age 16.68**	**Age 17.84**	**Age 18.65**	**Age 21.95**	**Age 22.88**	**Age 23.8**
Age 10.65	-								
Age 12.81	0.361*	-							
Age 13.84	0.271*	0.528*	-						
Age 16.68	0.233*	0.349*	0.397*	-					
Age 17.84	0.202*	0.297*	0.365*	0.502*	-				
Age 18.65	0.180*	0.290*	0.328*	0.490*	0.544*	-			
Age 21.95	0.178*	0.268*	0.283*	0.406*	0.424*	0.454*	-		
Age 22.88	0.187*	0.260*	0.301*	0.424*	0.396*	0.466*	0.618*	-	
Age 23.8	0.171*	0.264*	0.320*	0.409*	0.402*	0.462*	0.569*	0.664*	-

Table 3.3: Correlations between the SMFQ across the nine occasions. SMFQ: Short mood and feelings questionnaire. * denotes that correlations were $p < .0001$.

3.3 Data considerations

There are several considerations to be made with regards to the ALSPAC data and depressive symptoms that are important with regards to this thesis. As shown in table 3.2, ALSPAC is subject to attrition as the sample size for individuals with the SMFQ data decreased throughout the study from 7,354 at age 10 to 3,915 at age 24. An exploration with complete case analysis showed that the overall pattern of the SMFQ across the nine occasions was attenuated compared to the overall pattern shown in figure 3.2. As shown in figure 3.3, the shape of the SMFQ in ALSPAC was similar to the overall pattern, but for this complete case analysis, there were lower estimates. This supports the idea that individuals with greater depressive symptoms are more likely to drop out of the study. A further discussion on how I dealt with this issue is described later on in chapter 4. A more thorough discussion about how this may impact on the thesis is discussed in the conclusions chapter.

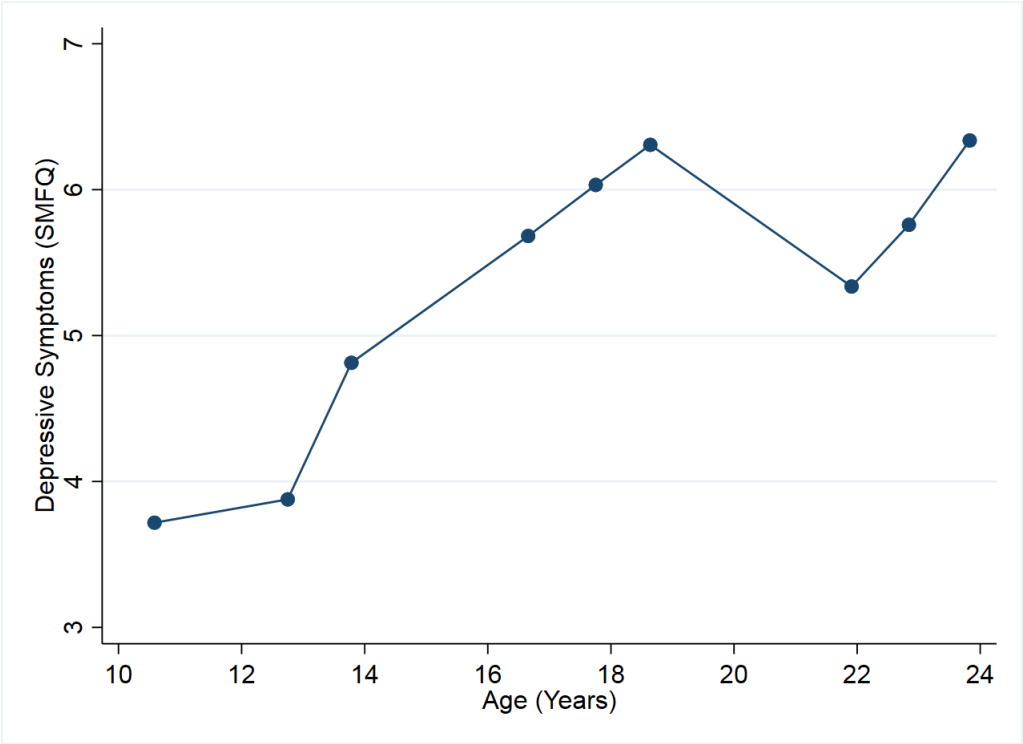


Figure 3.4: The mean depressive symptoms scores at each occasion as measured by the short mood and feelings (SMFQ) for individuals who answered every SMFQ assessment (i.e., complete case analysis).

Additionally, as shown in table 3.4 with the column percentages, there were demographic differences between individuals who completed the SMFQ at both ages 10 and 24, compared to those who only completed the SMFQ at age 10, with this latter group more likely to be male, have mothers with poorer educational attainment and lower occupational status, and have younger mothers. Given that some of

demographics are risk factors for depression, it may mean that depressive symptoms estimates presented in this thesis are lower than what they should be if there are missing data, that are not missing at random. Therefore these estimates may be more conservative due to more depressed individuals missing from the study.

This thesis focuses on trajectories of depressive symptoms and it is possible to estimate trajectories using at least one measure of depressive symptoms, as it is possible to estimate a trajectory using this information and thus maximise statistical power (I will discuss this method in the next chapter and how potential biases may be addressed). Thus, it is important to examine how individuals who have any SMFQ data in ALSPAC may differ from those who have not responded to any SMFQ assessments. A brief exploration of these data shows that the demographic information of individuals who have completed at least one assessment of the SMFQ varies from those who have not completed any assessments. Table 3.5 highlights these differences, but it is important to note that individuals without any SMFQ measures were also more likely to be male, have mothers with poorer educational attainment and lower occupational status at birth, be the third + born child and have a younger mother. I return to the issue of missing/non-random data in the next chapter.

	SMFQ at 10 and 24	SMFQ at 10 but not 24	x^2, p
Sex (n=7,359)			
Males n (%)	1,118 (35.6)	2,508 (59.4)	407.54, <.001
Females n (%)	2,020 (64.4)	1,713 (40.6)	
Maternal Education (n=6,723)			
A Level or Higher n (%)	1,442 (49.2)	1,418 (37.4)	137.18, <.001
O Level n (%)	1,016 (34.7)	1,368 (36.1)	
<O Level n (%)	472 (16.1)	1,007 (26.5)	
Maternal occupational Status (n=5,811)			
Non-manual n (%)	1,165 (45.1)	1,264 (39.2)	20.64, <.001
Manual or lower n (%)	1,419 (54.9)	1,963 (60.8)	
Parity (n=6,749)			
First Born n (%)	1,410 (48.4)	1,701 (44.4)	11.48, =.003
Second Born n (%)	1,024 (35.1)	1,421 (37.0)	
Third Born + n (%)	481 (16.5)	712 (18.6)	
Maternal Age at Pregnancy (n=6,983)			
<25 Years n (%)	372 (12.4)	675 (16.9)	47.39, <.001
25-29 n (%)	1,161 (38.8)	1,644 (41.2)	
30-34 n (%)	1,041 (34.8)	1,253 (31.4)	
35+ n (%)	416 (13.9)	421 (10.5)	

Table 3.4: Participant demographics for individuals with SMFQ at both 10 and 24 years compared to SMFQ at only 10 years. Pearson's chi-squared tests (x^2) used to highlight differences between participant demographics and individuals having both data.

	Included in Analysis	Excluded in Analysis	x^2, p
Sex (n=14,854)			
Males n (%)	4,495 (47.9)	3,140 (57.5)	128.98, <.001
Females n (%)	4,899 (52.1)	2,320 (42.5)	
Maternal Education (n=12,493)			
A Level or Higher n (%)	3,453 (40.9)	957 (23.7)	566.51, <.001
O Level n (%)	2,380 (35.3)	1,347 (33.3)	
<O Level n (%)	2,016 (23.8)	1,740 (43.0)	
Maternal occupational Status (n=10,118)			
Non-manual n (%)	2,940 (40.8)	841 (28.8)	126.95, <.001
Manual or lower n (%)	4,263 (59.2)	2,074 (71.2)	
Parity (n=13,124)			
First Born n (%)	3,918 (45.9)	1,955 (42.5)	54.16, <.001
Second Born n (%)	3,041 (35.7)	1,547 (33.7)	
Third Born + n (%)	1,569 (18.4)	1,094 (23.8)	
Maternal Age at Pregnancy (n=14,076)			
<25 Years n (%)	1,531 (17.3)	1,830 (35.2)	652.28, <.001
25-29 n (%)	3,513 (39.6)	1,927 (37.0)	
30-34 n (%)	2,809 (31.7)	1,069 (20.5)	
35+ n (%)	1,019 (11.4)	378 (7.3)	

Table 3.5: Pearson's chi-squared tests (x^2) used to highlight differences between participant demographics and individuals having at least one measure of the SMFQ.

3.4 Statistical methods

To explore trajectories of depressive symptoms, this thesis uses quantitative methods such as multilevel growth-curve modelling (to create population averaged trajectories) and growth mixture modelling (to compose multiple subpopulation trajectories). As discussed in chapter 2, these methods are useful for examining trajectories of depressive symptoms as they quantify how depressive symptoms change over time, but can be stratified to explore continuous and discrete heterogeneity between individual person trajectories, which can help answer substantively interesting questions regarding the aetiology of varying trajectories of depressive symptoms.

3.4.1 Multilevel growth-curve models

Multilevel growth-curve modelling [59, 131], is particularly effective for exploring trajectories of depressive symptoms as multilevel analysis is an appropriate method for handling longitudinal data. Traditional regression analysis assumes that responses from individuals (having adjusted for any covariates) are uncorrelated and independent of one another. However, with longitudinal data, the responses are not independent. Instead they are correlated as measures from the same individual will be more alike compared to measures from different people. This is graphically depicted in figure 3.4. Multiple measurements of depressive symptoms for person 1 (P1) are expected to be more alike compared to measurements from person 2 (P2). Examining longitudinal data with traditional regression analysis will naively assume multiple measures on the same individual are independent, and therefore result in biased standard errors (typically standard errors which are too small potentially leading to Type I errors of inference).

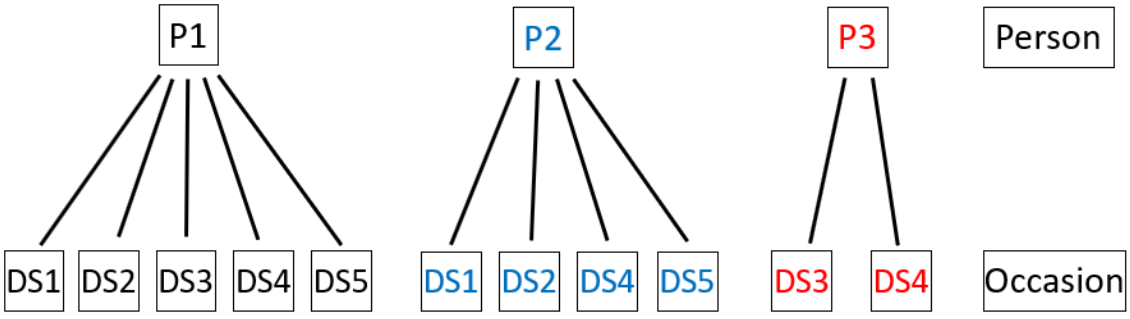


Figure 3.5: Multiple measurements from the same individual are more alike than multiple assessments from different individuals. P = Person; DS = Depressive symptoms.

Throughout this thesis, I use equations to define multilevel growth-curves for estimating trajectories of depressive symptoms. Let's first consider a very basic

multilevel growth-curve to estimate a random intercept and random linear slope trajectory of depressive symptoms:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + u_{0j} + u_{1j} t_{ij} + e_{ij} \tag{3.1}$$

where y_{ij} is the depressive symptom score and t_{ij} is the age for individual j at occasion i. Age can be set in days, months or years and can be centred to a specific age i.e., 0 – the timing of the first assessment. I will discuss this more in the next chapter with an example. Here, β_0, β_1 denote the associated regression coefficients for the intercept and slope terms, and u_{0j}, u_{1j} are the random intercept and linear effects of age that allow each individual to have their own trajectory. The occasion-specific residual e_{ij} allows the depressive symptom scores to deviate from the individual-specific trajectories, so this captures the degree of within-individual variability.

The random effects are assumed bivariate normal distributed with zero mean vector and constant covariance matrix:

$$\begin{pmatrix} u_{0j} \\ u_{1j} \end{pmatrix} \sim N \left\{ \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma^2_{u0} & \\ \sigma_{u01} & \sigma^2_{u1} \end{pmatrix} \right\} \tag{3.2}$$

The elements of the covariance matrix summarise the degree to which individual-specific trajectories vary around the population-averaged trajectories – so showing how each person deviates from the population average with regards to their intercept, slope and intercept-slope covariance.

The residuals are assumed normally distributed with zero mean and constant variance:

$$e_{ij} \sim N\left(0, \sigma^2_{ej}\right) \tag{3.3}$$

However, as noted earlier in this chapter, the change in depressive symptoms is rarely linear. In fact, figure 3.2 demonstrates that the overall pattern of depressive symptoms is distinctly non-linear. To better capture this non-linearity, it is possible to enter time as a higher order polynomial (e.g., quadratic, cubic, or quartic). In the next chapter, I will expand upon the multilevel growth-curve model in order to

take this non-linearity into account.

Throughout this thesis I use these multilevel growth-curves to estimate trajectories. In each chapter that uses this method to examine the association with a risk factor, I incorporate a risk factor that is interacted with the trajectories to examine how that risk factor (i.e., genetic risk or childhood trauma) affects change over time. I provide further information on how this is done in each of these chapters.

3.4.2 Growth mixture modelling

An alternative approach for estimating trajectories of depressive symptoms is to use growth mixture modelling (GMM) to create a number (e.g., 2-5) of subpopulation trajectories (or latent classes) within a population corresponding to unobserved groups [41, 55]. As highlighted in chapter 2, the GMM approach extends the growth curve model to create multiple trajectories that follow distinct developmental trajectories and this approach is popular for examining trajectories of depressive symptoms as it is useful for creating discrete patterns of mood. As highlighted in the literature review, these may be useful for qualitatively describing groups of individuals such as those with consistently low symptoms (stable low), or those with consistently high symptoms (high-persistent). In this thesis, I use the GMM approach to stratify individual's into multiple subpopulation trajectories using posterior probabilities [40], which essentially means that each person has a probability of belonging to every trajectory or class, but the trajectory with the highest probability determines the classification for that individual. As stated in the literature review, GMM is an extension of latent class growth analysis (LCGA) as it allows for within-trajectory variability which means that each individual can have their own trajectory within each group. Depressive symptoms are heterogeneous, especially around adolescence and so this thesis will not use the LCGA approach. The simplest form of the GMM for creating trajectories of depressive symptoms can be defined by:

$$y_{ij|C_j=k} = \beta_0^{[k]} + \beta_1^{[k]} t_{ij} + u_{0j}^{[k]} + u_{1j}^{[k]} t_{ij} + e_{ij}^{[k]} \tag{3.4}$$

where y_{ij} is the depressive symptom score and t_{ij} is the linear age term for individual j at occasion i. Let C_j denote the latent class for which individual j belongs. These classes are indexed by $k = 1, \ldots, K$. Additionally, $\beta_0^{[k]}$ and $\beta_1^{[k]}$ denote the associated regression coefficients for the intercept and slope in class k, whilst $u_{0j}^{[k]}$ and $u_{1j}^{[k]}$ are the random intercept and slope effects that allow each individual to have their own trajectory. Like the multilevel growth curve model,

$e_{ij}^{[k]}$ is the occasion specific residual which is allowed to vary within trajectories. As with the multilevel growth-curve model, these models can be expanded to allow for non-linearity, which I will expend on in the next chapter.

After determining the optimal number of trajectories, covariates (risk factors) were added into the model to examine risk factors for varying trajectory membership. Odds ratios (ORs) and their corresponding 95% confidence intervals (95% CI) were derived from multinomial logistic regressions, where the trajectory with the largest sample size was used as the reference.

In the following chapter I go on to use this method and provide more information about how the variances can be constrained and relaxed, depending on the data available. Additionally, I also use the multilevel growth-curve model to show how both trajectories can be created in ALSPAC and how they compare and contrast one another. In later chapters, I also show how risk factors can be included into these models, which will identify which genetic and environmental risk factors are associated with these trajectories of depressive symptoms.

3.5 Chapter summary

This chapter has introduced the data and methods used throughout this thesis. I have demonstrated that ALSPAC is one resource that can be used to examine the longitudinal nature of depressive symptoms and can be used for examining the main aim of this thesis: exploring associations between genetic and environmental risk factors and trajectories of depressive symptoms. However, I have also highlighted several key issues (i.e., missing data and bias) that should be considered throughout this thesis. I will return to the issue of missing data in the next chapter and discuss the implications in the conclusions chapter. The following chapters are now based upon empirical studies that utilise this data for examining the association between genetic and environmental risk factors and trajectories of depressive symptoms. In particular, the next chapter will derive and model these trajectories in ALSPAC (which can then be used in subsequent studies), whilst chapter 5 will use the multiple-subpopulation approach and chapters 6, 7 and 8 will use the population-averaged approach. Chapters 5, 6, 7 and 8 will all examine varying genetic and environmental risk factors and their association with trajectories of depressive symptoms.

Chapter 4

Identifying Trajectories of Depressive Symptoms Across Adolescence and Young Adulthood

4.1 Chapter outline

Before it is possible to examine genetic and environmental contributions to trajectories of depressive symptoms (chapters 5, 6, 7 and 8), it is first important to model and identify the trajectories themselves within the ALSPAC data. The literature review in chapter 2 highlighted two issues that are worth noting here: 1) whilst there are common patterns of trajectories between studies and cohorts, it is important to adequately model the trajectory according to the data available; 2) there are two popular methods that can be used to derive trajectories: one that creates population averaged trajectories (using multilevel growth-curve modelling) another that creates multiple-subpopulation trajectories (using growth mixture modelling). In this chapter, I aim to derive trajectories of depressive symptoms within ALSPAC using both approaches to explore two different types of trajectories of depressive symptoms. This will be achieved in order to answer the first research objective: "what are the varying patterns of longitudinal depressive symptoms across adolescence?". These results can then be used to explore the association between genetic and environmental risk factors and trajectories of depressive symptoms in the subsequent chapters - thus this chapter is the foundation for the rest of the thesis.

4.2 Introduction

Examining the longitudinal nature of depressive symptoms can be complex, especially during adolescence as this developmental period marks a stage where depression will commonly onset [16], and is characterised by abrupt changes in depressive mood [103]. As discussed in the literature review, growth curve modelling is one approach that can be used to adequately capture the nature and extent of changes in depressive symptoms over time.

The literature review identified many studies that use a growth curve modelling approach to identify trajectories of depressive symptoms. As discussed in the data and methods chapter (chapter 3), ALSPAC is one of the few cohorts that has repeated assessments of depressive symptoms (the short mood and feelings questionnaire [SMFQ]) across important stages of development (childhood to adolescence, adolescence to young adulthood). Additionally, few studies have as many assessments of depressive symptoms (currently nine occasions), which can help capture some of these abrupt nuanced changes in depressive symptoms and give inference on the patterns, onset and severity of depression.

Using ALSPAC data, trajectories of depressive symptoms have been derived in several ways. For example, within the population-averaged approach for trajectories, one study derived trajectories separately for males and females in order to predict later alcohol use. They fitted a quadratic polynomial model yet were only able to use data up to the ages of 18 [108]. Regardless of the sex differences observed, Edwards and colleagues found that depressive symptoms were distinctly non-linear, and showed patterns of increasing and decreasing depressive symptoms across the time course that were sex specific (i.e., males tended to have symptoms that increased, whilst females had symptoms that increased until the age of approximately 17, where symptoms then began to decrease). Additionally, using similar data and methods with data up to the age of approximately 18, several studies have shown that depressive symptoms can increase and change the rate at which they increase with regards to the age of menarche in females [132, 133]. These studies imply that when examining changes within population-averaged trajectories, it is important to consider the non-linearity for how depressive symptoms may change over development. As shown in the data and methods chapter, the depressive symptoms in ALSPAC begin to decrease after the age of 18 to the ages of 22, before increasing again until the age of 24. As no studies have examined the change in depressive symptoms in ALSPAC post age 18, it is important to identify why this patter is occurring and if risk factors for adolescent depressive symptoms are the same or are maintained throughout young adulthood and beyond. Identifying the longitudi-

nal nature of depressive symptoms is important for understanding for epidemiology of depressive symptoms, but examining if (different) risk factors have long lasting consequences that occur in both adolescence and young adulthood (or certain risk factors that are specific to one period) is important for developing treatments and interventions.

It is also important to highlight that several other studies have used the multiple-subpopulation trajectories approach (i.e., grouping the population into qualitatively distinct trajectories) to derive trajectories of depressive symptoms in ALSPAC. For example, one study found that between the ages of 10 and 18, it was possible to identify 4 qualitatively distinct trajectories of depressive symptoms that were described as "stable low", "stable moderate", "moderate increasing" and "consistently high" [75]. More recently, using the binary measures of the SMFQ (where the cut-off point of more than or equal to 11 is used; see chapter 3 for details), one study has identified three distinct trajectories with similar data that were described as "persistently low", "later-adolescent onset" and "early-adolescence onset" [87]. The nature of these trajectories also suggests that the change in depressive symptoms is non-linear and may be characterised by the onset, chronicity and severity of symptoms across development. Thus, the multiple-subpopulation approach gives a similar but also alternative view of how trajectories of depressive symptoms can be modelled, compared to the population-averaged approach. Similar in that the change in depressive symptoms are unlikely to be linear over time, but different in that the heterogeneity of these trajectories is classified by discrete groups, rather than continuous heterogeneity and it is possible to identify groups of individuals (i.e., those with increasing symptoms at later or early adolescence or those with chronically severe symptoms) that may not be visible in the population averaged approach.

It is important to highlight that whilst only a handful of studies have utilised ALSPAC to derive trajectories of depressive symptoms for examining substantively interesting questions regarding the longitudinal nature of depressive symptoms, this is likely a result of available data rather than a lack of interest (as the three latter waves were recently released post late-2016). Nevertheless, the release of this new data provides an exciting opportunity to explore how depressive symptoms change over the later stages of adolescence and into young adulthood (and downstream allows researchers to explore if certain risk factors are differentially associated with greater levels of depressive symptoms at different developmental periods (i.e., adolescence or young adulthood or both). With regards to this thesis, to efficiently explore the genetic and environmental contributions to trajectories of depressive symptoms, these trajectories must be suitably modelled and identified in ALSPAC, before risk factors can be included into the analysis. Thus, this chapter forms the

foundations for this thesis as the remaining chapters will all utilise the trajectories estimated here. Therefore, the remainder of this chapter describes the methods used to capture these changes in depressive symptoms, using the two different modelling approaches.

4.3 Methods

Sample

As described in the data and methods chapter (chapter 3), the data used in this study came from the Avon Longitudinal Study of Parents and Children (ALSPAC). The response is depressive symptoms measured on nine occasions using the short mood and feelings questionnaire (SMFQ).

Multilevel growth-curve models

As described in the data and methods chapter, multilevel growth-curve modelling [59, 131] can be used to derive population-averaged trajectories of depressive symptoms. In the previous chapter I described this method for a very simple random intercept and random slope trajectory model (equation 3.1), but as discussed there and in the literature review (chapter 2), the change in depressive symptoms is unlikely to be linear and will therefore require a more advanced modelling of the relationship between the response and age to capture this non-linearity. To do this, age can be entered as a quadratic, cubic, quartic or higher-order polynomial [102, 108]. However, as shown in figures 3.2 and 3.4 (in the previous chapter), there appear to be three inflection points in depressive symptoms within ALSPAC (i.e., ages where depressive sympotms tend to go up or down). For instance, depressive symptoms at age 10 decrease until age 12, then they begin to increase until about the age of 18. From here, depressive symptoms decrease until the age of about 22, where they begin to increase again post the age of 24. This latter increase between the ages of 22 and 24 suggest that a quartic age polynomial is required. To demonstrate this, I estimated a multilevel growth-curve model using a quartic polynomial model which takes the following form:

$$\begin{aligned} y_{ij} = {} & \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4 \\ & + u_{0j} + u_{1j} t_{ij} + u_{2j} t_{ij}^2 + u_{3j} t_{ij}^3 + u_{4j} t_{ij}^4 \\ & + e_{ij} \end{aligned} \tag{4.1}$$

where y_{ij} is the depressive symptom score and t_{ij}, t_{ij}^2, t_{ij}^3, and t_{ij}^4 are the linear, quadratic, cubic and quartic age terms for individual j at occasion i. Additionally, β_0, β_1, β_2, β_3, and β_4 denote the associated regression coefficients for the intercept and age terms. The u_{0j}, u_{1j}, u_{2j}, u_{3j} and u_{4j} are the random intercept, linear, quadratic, cubic and quartic individual-specific effects that allow each individual to have their own trajectory, and e_{ij} is the occasion-specific residual. Prior to constructing the quartic polynomial, age was grand mean centred around age 16.53 (the mean age of assessments) in order to improve interpretation and aid in convergence. Specifically, the interpretation of the intercept and intercept variance will describe the population average depression and between-subject variance evaluated at age 16.53.

The random effects are assumed multivariate normal distributed with zero mean vector and constant covariance matrix:

$$\begin{pmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \\ u_{4j} \end{pmatrix} \sim N \left\{ \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{u0}^2 & & & & \\ \sigma_{u01} & \sigma_{u1}^2 & & & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 & & \\ \sigma_{u03} & \sigma_{u13} & \sigma_{u23} & \sigma_{u3}^2 & \\ \sigma_{u04} & \sigma_{u14} & \sigma_{u24} & \sigma_{u34} & \sigma_{u4}^2 \end{pmatrix} \right\} \tag{4.2}$$

The elements of the covariance matrix summarise the degree to which individual-specific trajectories vary around the population-averaged trajectory. The residuals are still assumed normally distributed with zero mean and constant variance:

$$e_{ij} \sim N(0, \sigma_e^2) \tag{4.3}$$

All models were fit by maximum likelihood estimation and were conducted using Stata 15 (StataCorp, College Station, TX, USA) using the user-written runmlwin command [134], which calls the standalone multilevel modelling package MLwiN v3.01 (www.cmm.bristol.ac.uk/MLwiN/index.shtml).

Multilevel comparisons

To demonstrate that the quartic polynomial growth-curve model was the preferred model to use throughout this thesis, I also estimated linear, quadratic and cubic polynomial trajectory models and compared them to one another using likelihood-

ratio tests and information criteria (deviance, Akaike information criterion [AIC] and Bayesian information criterion [BIC]), as recommended by Singer and Willett [50]. As a further check, I also explored comparisons between other non-linear models such as fractional polynomials, that have been used in other forms of childhood growth [61, 135]. Results from these further checks can be found in appendix 4.

4.3.1 Growth mixture modelling

The alternative approach to growth curve modelling considered here is to derive multiple-subpopulation trajectories using growth mixture modelling (GMM). Ifit these models by maximum likelihood estimation as implemented in Mplus v7 [41]. I introduced this method in the previous chapter, by focusing on a very simple model that estimated K trajectories or classes such as "stable low" or "increasing, with linear change (shown in equation 3.4). Let us now consider a more advanced approach that allows for trajectories (or classes) to be non-linear (as highlighted in the literature review), so that it is possible to derive some of these potentially interesting characteristics such as age of onset or severity. To do this, I estimated trajectories with intercept, slope and quadratic growth factors for each class. This model can be defined by:

$$y_{ij|C_j=k} = \beta_0^{[k]} + \beta_1^{[k]} t_{ij} + \beta_2^{[k]} t_{ij}^2 + u_{0j}^{[k]} + u_{1j}^{[k]} t_{ij} + u_{2j}^{[k]} t_{ij}^2 + e_{ij}^{[k]} \tag{4.4}$$

where y_{ij} is the depressive symptom score and t_{ij}, t_{ij}^2, are the linear and quadratic age terms for individual j at occasion i. Let C_j denote the latent class for which individual j belongs. These classes are indexed by $k = 1, \ldots, K$. Additionally, $\beta_0^{[k]}$, $\beta_1^{[k]}$ and $\beta_2^{[k]}$ denote the associated regression coefficients for the intercept, linear and quadratic age terms in class k, whilst $u_{0j}^{[k]}$, $u_{1j}^{[k]}$ and $u_{2j}^{[k]}$ are the class specific random intercept, linear and quadratic individual specific effects that allow each individual to have their own trajectory. Thus, we have K sets of individual random effects, each with their own distributional assumptions:

$$\begin{pmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \end{pmatrix} \sim N \left\{ \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma^2_{u0[k]} & & \\ \sigma_{u01[k]} & \sigma^2_{u1[k]} & \\ \sigma_{u02[k]} & \sigma_{u12[k]} & \sigma^2_{u2[k]} \end{pmatrix} \right\} \tag{4.5}$$

Like the multilevel growth curve model, $e_{ij}^{[k]}$ is the class specific occasion residual:

$$e_{ij}^{[k]} \sim N(0, \sigma_e[k]^2) \tag{4.6}$$

In order to reduce convergence issues, the individual-level random effects variance-covariance matrix was constrained to be equal across the latent classes, which is common in this methodology [41], the residual variance was constrained equal across classes as with previous research [130].

As is typical in GMM, I built a stepwise model starting with a single trajectory and continued to add trajectories into the model until the optimal number of trajectories was reached [40]. To assess this optimum, I used a range of criteria including: lowest sample-size-adjusted Bayesian Information Criterion (ssaBIC; which based on the log-likelihood penalised for model complexity as captured by the number of parameters [136]), and hypothesis testing to help model choice by comparing model fit for k versus k-1 trajectories, using the adjusted likelihood ratio test (LRT) and bootstrap likelihood ratio test (BLRT) proposed by Lo-Mendell-Rubin [137]. I chose to use a variety of model fit statistics as there is no universal appraised approach and that support for the "preferred" number of trajectories is often achieved through agreement of numerous fit statistics.

4.3.2 Missing data

Missing data in the multilevel growth-curve models and GMM were handled using full information maximum likelihood estimation (FIML), which assumes that the data are missing at random [138, 139]. This means that once we account for the series of depressive symptoms scores on each individual that we do observe, the probability that they are missing any subsequent measurement in the data does not depend on their unknown level of depressive symptoms at that occasion. This method is common in growth-curve research provides similar estimates to imputation approaches [138], providing the assumption of missing at random is still held. To maximise the data, I included individuals into these analysis if they had at least one measurement of depression symptoms [130] as this boosts the effectiveness of the FIML approach by utilising all the available data.

4.4 Results

4.4.1 Sample

There were 9,399 individuals who had at least one measurement of depressive symptoms, that were used to create trajectories in the population-averaged and multiple trajectories approach. I describe the results for each approach in the following section.

4.4.2 Multilevel growth-curve models

When estimating the multilevel growth curves, the quartic polynomial model best fitted the data compared to the linear, quadratic and cubic polynomial models as assessed by likelihood ratio tests and information criterion. Building a stepwise model, the quadratic model was preferred to the linear model (x^2 = 1383.27, p <.001), the cubic model was preferred to the quadratic model (x^2 = 394.1, p <.001), and the quartic model preferred to the cubic model (x^2 = 858.25, p <.001). As shown in table 4.1. the model fit (as assessed by deviance, AIC and BIC) were all lower for the quartic model. The quartic model also observably fitted the data best, capturing the changes in depressive symptoms across development, including three turning points, as shown in figure 4.1. Comparisons between the quartic polynomial model and the fractional polynomials revealed the quartic polynomial model had better model fit (see table 4.2. and appendix 4 for further details).

	Linear Model			Quadratic Model			Cubic Model			Quartic Model		
Parameter	**Estimate**	**SE**	***p***	**Estimate**	**SE**	***p***	**Estimate**	**SE**	***p***	**Estimate**	**SE**	***p***
$\beta 0$ Intercept	5.473	0.038	<.001	5.848	0.05	<.001	5.858	0.051	<.001	6.279	0.057	<.001
$\beta 1$ Age (linear)	0.219	0.006	<.001	0.238	0.006	<.001	0.325	0.014	<.001	0.366	0.014	<.001
$\beta 2$ Age^2 (quadratic)	-	-	-	-0.02	0.001	<.001	-0.016	0.001	<.001	-0.099	0.004	<.001
$\beta 3$ Age^3 (cubic)	-	-	-	-	-	-	-0.002	0.0003	<.001	-0.005	0.0004	<.001
$\beta 4$ Age^4 (quartic)	-	-	-	-	-	-	-	-	-	0.002	0.0001	<.001
Intercept var	9.255	0.199	-	14.172	0.33	-	13.985	0.329	-	16.907	0.412	-
Intercept/slope cov	0.72	0.022	-	0.813	0.03	-	1.045	0.062	-	1.271	0.072	-
Slope var	0.105	0.004	-	0.11	0.005	-	0.352	0.024	-	0.408	0.024	-
Intercept/quadratic cov	-	-	-	-0.158	0.007	-	-0.145	0.007	-	-0.493	0.025	-
Slope/quadratic cov	-	-	-	-0.002	0.001	-	-0.006	0.002	-	-0.03	0.005	-
Quadratic var	-	-	-	0.003	0.0002	-	0.003	0.0002	-	0.028	0.002	-
Intercept/cubic cov	-	-	-	-	-	-	-0.007	0.001	-	-0.018	0.002	-
Slope/cubic cov	-	-	-	-	-	-	-0.005	0.001	-	-0.007	0.001	-
Quadratic/cubic cov	-	-	-	-	-	-	0.0002	0.00004	-	0.001	0.0001	-
Cubic var	-	-	-	-	-	-	0.0001	0.00001	-	0.0001	0.00002	-
Intercept/quartic cov	-	-	-	-	-	-	-	-	-	0.007	0.0005	-
Slope/quartic cov	-	-	-	-	-	-	-	-	-	0.0005	0.0001	-
Quadratic/quartic cov	-	-	-	-	-	-	-	-	-	-0.0004	0.00004	-
Cubic/quartic cov	-	-	-	-	-	-	-	-	-	-0.00001	0.000003	-
Quartic var	-	-	-	-	-	-	-	-	-	0.00001	0.000001	-
Residual variance	13.898	0.115	-	12.69	0.116	-	12.364	0.126	-	11.594	0.128	-
ICC	0.54			0.55			0.53			0.59		
Deviance	254892.83			252509.56			253115			252257.21		
AIC	254904.8			253529.6			253145.5			252299.2		
BIC	254957			253616.5			253275.8			252481.7		

Table 4.1: Model estimates between trajectories. Note: SE: Standard error; p: p-value; Var: Variance; Cov: Covariance; ICC: Intraclass correlation; AIC: Akaike information criterion; BIC: Bayesian information criterion. Age was centered to 16.53 years, the mean age of all the assessments

The estimates for the quartic polynomial model are also given in table 4.1 and indicate that population averaged depressive symptom scores at age 16.53 were 6.28. These results combined with inspecting the plot of the population average trajectory in figure 4.1 suggest that from initially low levels of depressive symptoms around age 10, depressive symptoms began to increase towards the age of 18, before decreasing until the age of 22. From here, depressive symptoms then began to rise again.

Figure 4.2 shows the predicted population averaged trajectory for this quartic model now supplemented with 100 random individual trajectories surrounding the population averaged trajectory. The trajectories in the latter ages appeared to be "fanning out", which suggests that the trajectories were getting more heterogeneous at these later ages.

Model	**Deviance**	**AIC**	**BIC**
Linear Model	254892.8	254904.8	254957
Quadratic Polynomial	252509.6	253529.6	253616.5
Cubic Polynomial	253115	253145.5	253275.8
Quartic Polynomial	**252257.2**	**252299.2**	**252481.7**
Fractional Cubic Polynomial	252728.6	252758.6	252889.8
Fractional Quartic Polynomial	252279.7	252319.7	252493.5

Table 4.2: Comparison between polynomial models(n=9,399). Note: AIC: Akaike information criterion; BIC: Bayesian information criterion.

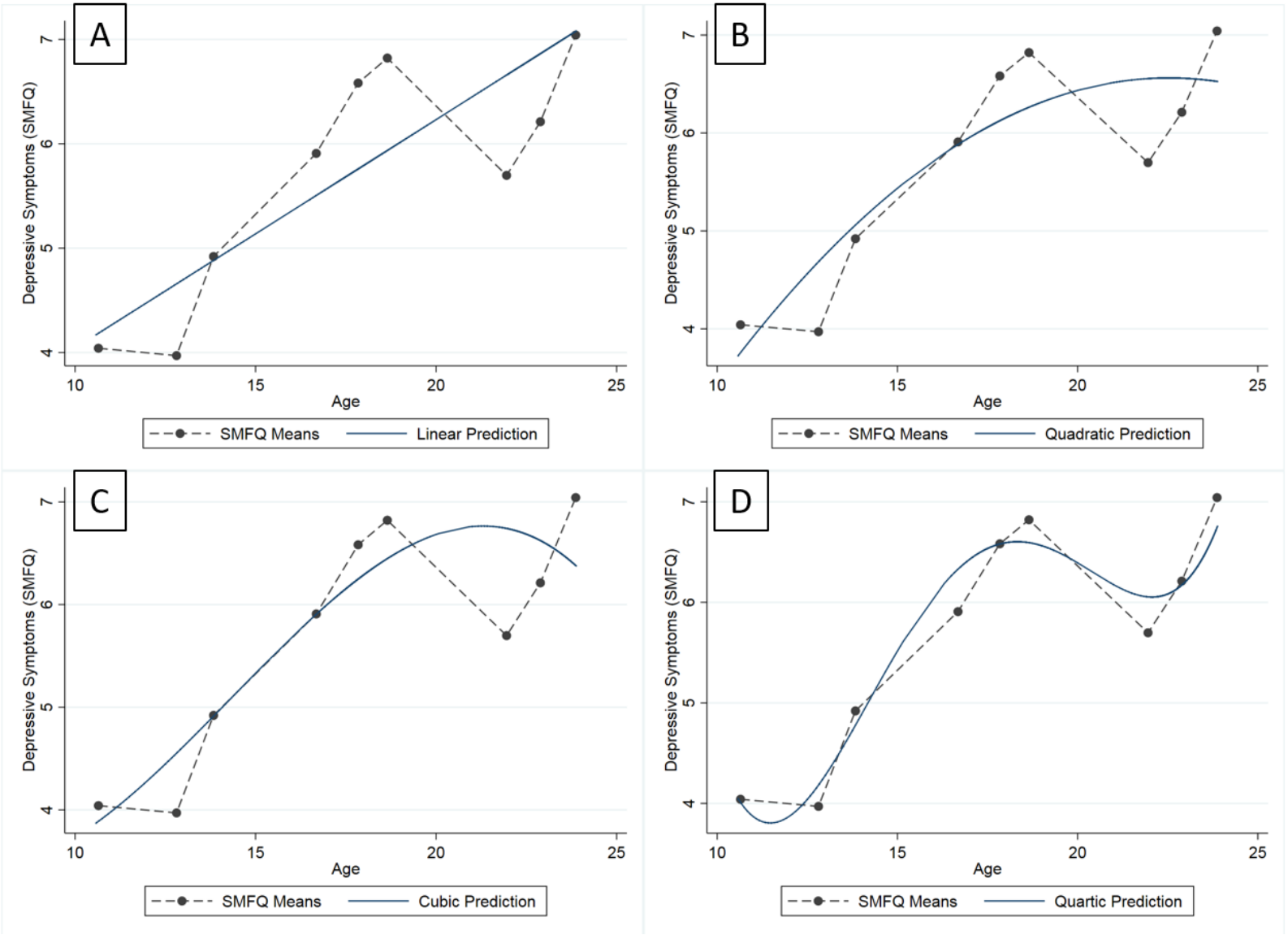


Figure 4.1: Comparisons between linear (A), quadratic (B), cubic (C) and quartic (D) polynomial models.

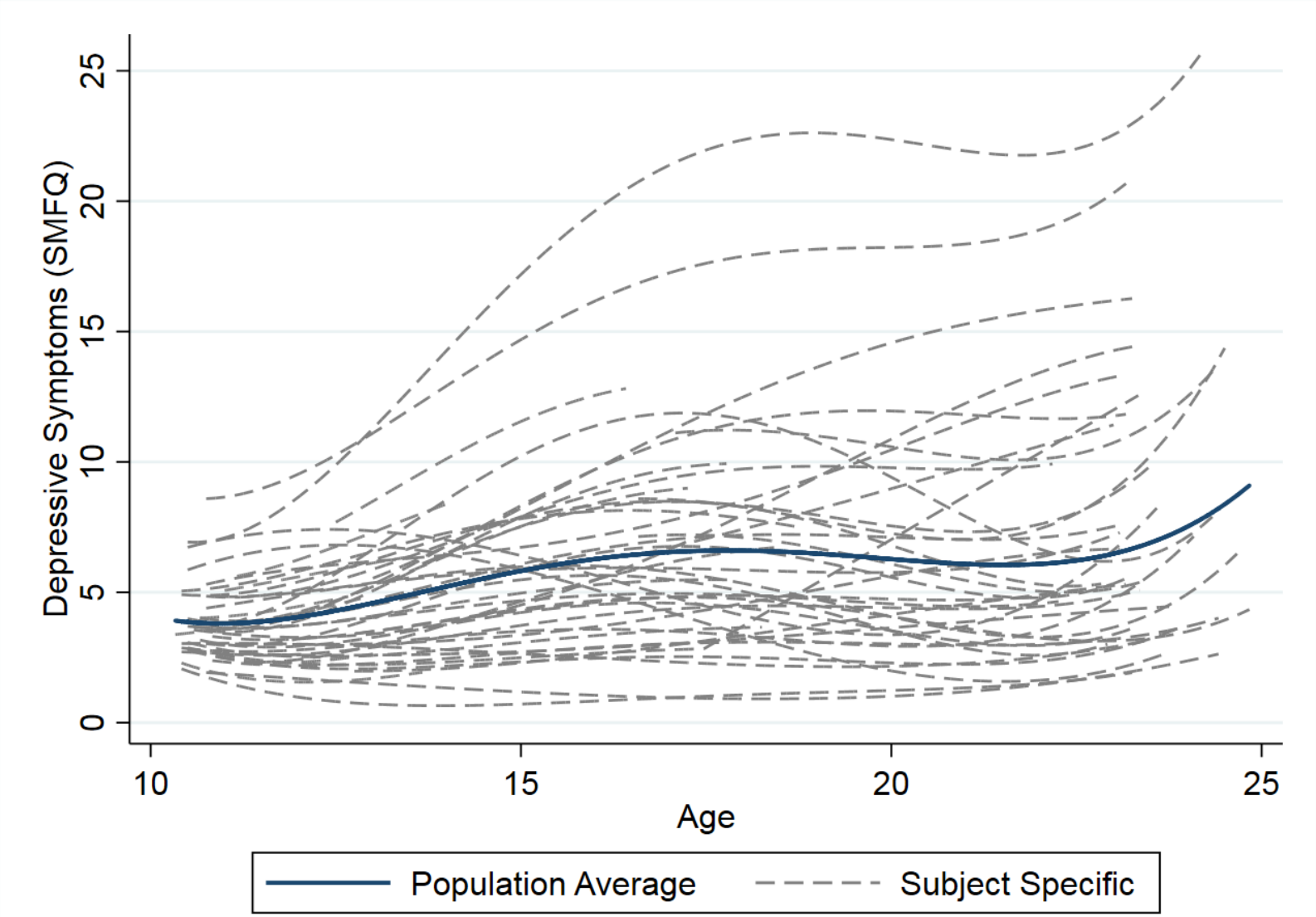


Figure 4.2: Quartic population averaged trajectory with a random 100 individual specific trajectories.

4.4.3 Growth mixture models

Whilst using the $k+1$ approach, there was evidence that five qualitatively distinct subpopulation trajectories of depressive symptoms best fitted the data in ALSPAC. As shown in table 4.3., the five trajectories model was preferred to both the four and six classes trajectories solutions. Adding classes generally resulted in better model fit (as shown by smaller ssaBIC). This suggested that multiple classes were preferred to a single unconditional model. However, adding classes also resulted in lower entropy, which is a marker for accuracy in the assignment of posterior class distributions (i.e., the certainty to which an individual belongs to a specific class). The LRT showed that adding a sixth class did not improve the model fit over and above the five-class solution. Taken all of this into consideration, I decided to settle on the five-class solution as class certainty and model fit are often regarded as the best indices of model selection in growth mixture models [139]. As shown in figure 4.3, the 5 trajectories can be described as the following: those who had consistently low levels of depression symptoms - stable low (black line: 70.5%/n=6627), individuals who started with low depression symptoms but rose throughout adolescence and young adulthood – early-adult onset (turquoise line: 11.6%/n=1087), individuals who experienced elevated levels of depression symptoms only during adolescence – adolescent limited (pink line: 9.4%/n=881), individuals who started with elevated levels of depression symptoms in childhood which decreased over time – childhood limited (yellow line: 5.1%/n=480) and individuals with moderate levels of depression symptoms that continued to rise and stay high across adolescence and into young adulthood – childhood persistent (purple line: 3.5%/n=324). Figure 4.3 shows all the estimated trajectories whilst, figure 4.4 and figure 4.5 show the estimated average trajectories with 100 individual specific observed and predicted trajectories for each latent class, respectively.

k	NP	ssaBIC	Entropy	LRT(p)	BLRT(p)
1	10	253634.62	-	-	-
2	11	252306.66	0.793	<.0001	<.001
3	15	251346.88	0.743	<.0001	<.001
4	19	250909.03	0.752	.1040	<.001
5	**23**	**250484.48**	**0.736**	**.0014**	**<.001**
6	27	250230.41	0.735	.0966	<.001

Table 4.3: Comparison between trajectory groups in the growth mixture model. Note: k: number of classes; NP: number of parameters; ssaBIC: sample size adjusted Bayesian Information Criterion; LRT: Lo-Mendell-Rubin likelihood ratio test; BLRT: bootstrap likelihood ratio test.

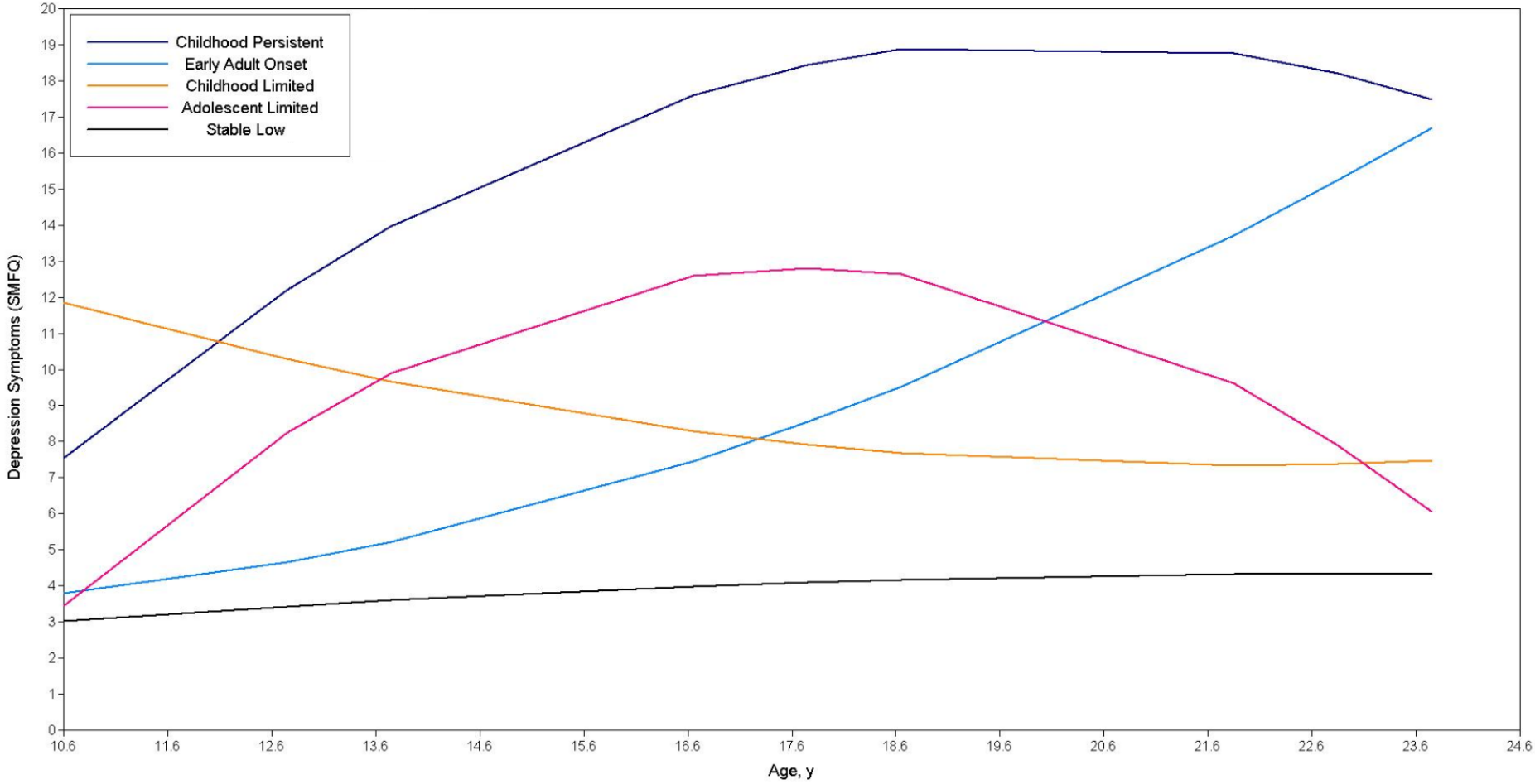
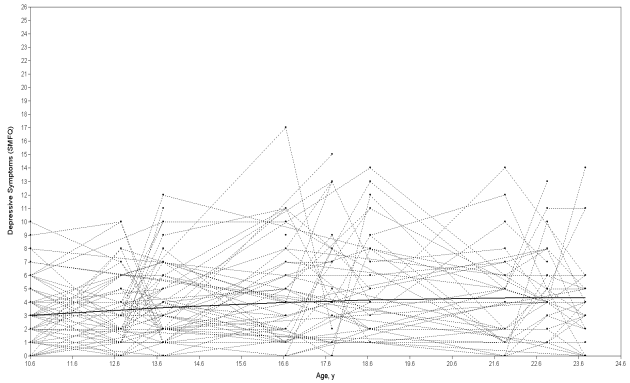
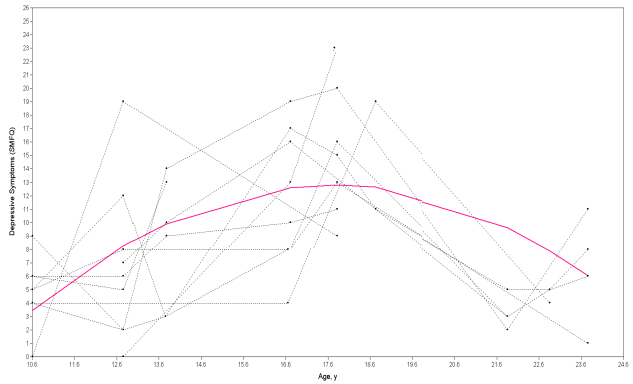


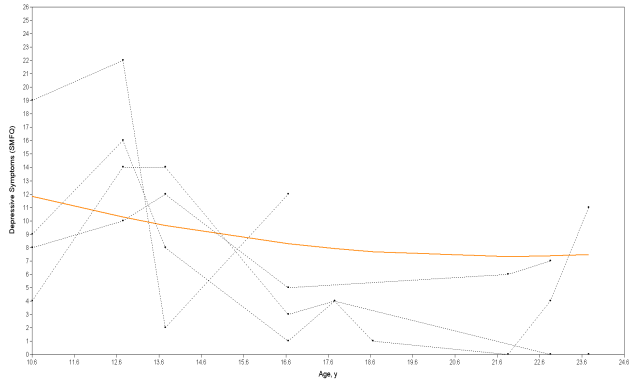
Figure 4.3: 5 trajectories from the growth mixture modelling in ALSPAC



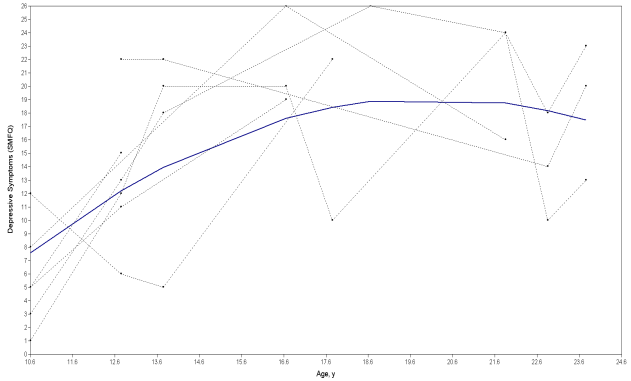
(a) Stable Low



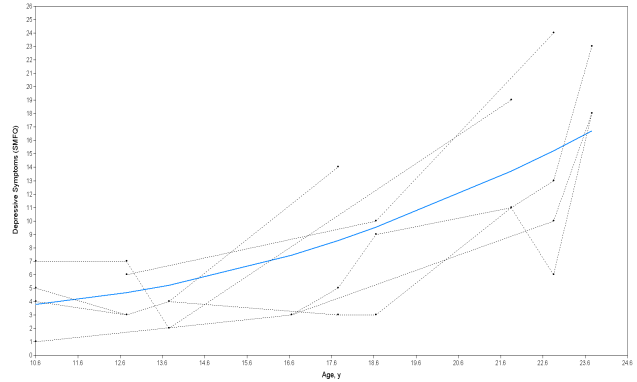
(b) Adolescent Onset



(c) Childhood Limited

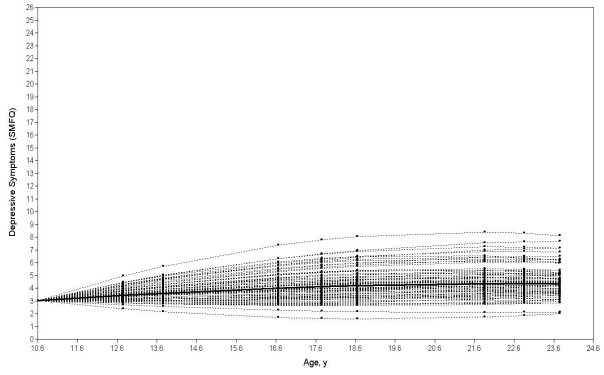


(d) Childhood Persistent

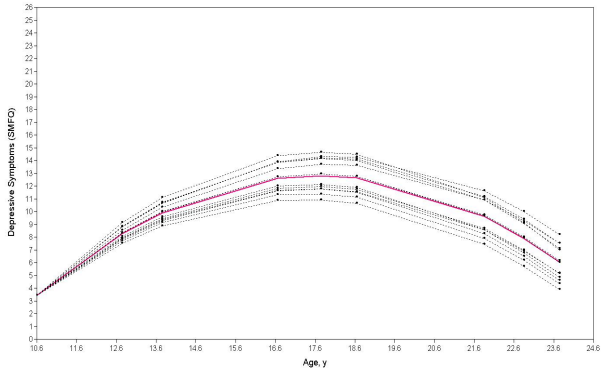


(e) Early Adult Onset

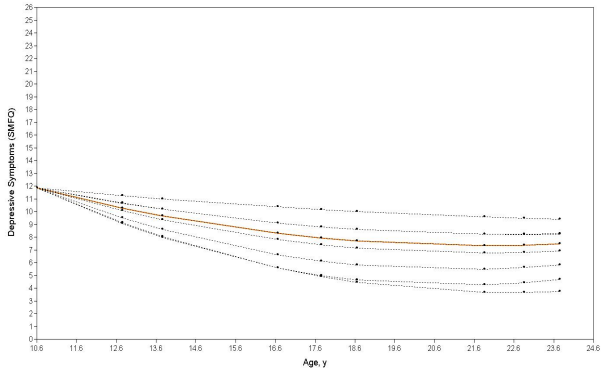
Figure 4.4: Observed trajectories from the GMM. A random subset of 100 observed individual trajectories assigned to the various trajectory groups.



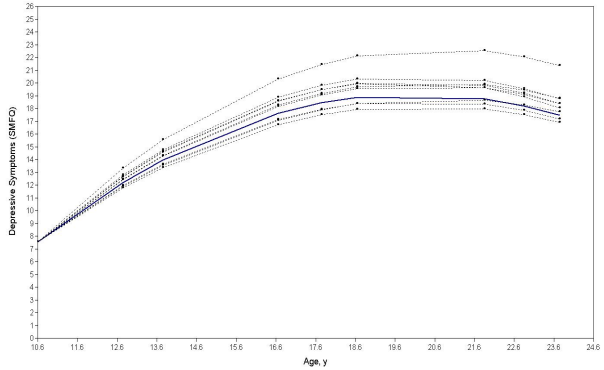
(a) Stable Low



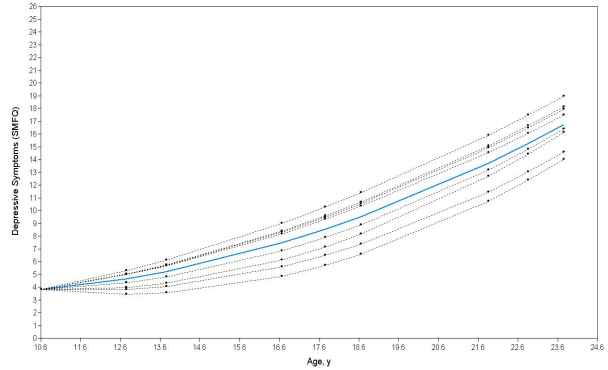
(b) Adolescent Onset



(c) Childhood Limited



(d) Childhood Persistent



(e) Early Adult Onset

Figure 4.5: Predicted trajectories from the GMM. A random subset of 100 predicted individual trajectories assigned the various trajectory groups.

4.5 Discussion

The analysis in this chapter has allowed me to identify trajectories of depressive symptoms using two different methodologies: the population averaged approach (within the multilevel growth-curve modelling framework) and the multiple-subpopulation trajectories approach (within the growth mixture modelling framework). For the population averaged approach, the analysis revealed that a quartic polynomial model best fitted the data, in preference to simpler polynomial models such as the linear, quadratic and cubic polynomial models. For the multiple trajectories approach, the analysis in this chapter revealed that a five-class quadratic trajectories solution bets fitted the data, in preference to a two, three, four or six class solution. For both approaches, the results were compared using a variety of model fit criterion and statistics.

4.5.1 Comparisons with previous research

Previous research examining depressive symptoms using the population averaged approach has normally utilised a quadratic or cubic polynomial model [101, 102]. With ALSPAC data, previous analysis has only tended to use a quadratic polynomial approach for estimating non-linear trajectories of depressive symptoms [108], as many studies have only had depressive symptoms data to the age of approximately 18. With the release of new data in ALSPAC, it was necessary to expand upon these previous models to capture this pattern of depressive symptoms from childhood to young adulthood.

4.5.2 Population-averaged trajectories in ALSPAC

The analysis in this chapter has shown that a quartic polynomial model is preferred to the simpler models and this was verified by both likelihood ratio tests and a series of information criterion. Also, it was possible to observably see that the quartic polynomial fitted the data better than the other models (as shown in Figure 4.1). It is important to state that no previous studies have gone beyond a cubic polynomial model whilst deriving trajectories of depressive symptoms. However, this is likely because very few studies have such frequent measures of depressive symptoms within such a short period. Other longitudinal studies such as the Add Health study [140], which has rich measures of depressive symptoms (as assessed by the CES-D) only has four assessments of data spanning a 20-year period. Other longitudinal studies such as the NLSCY [141], have similar waves of data (8 assessments over 14 years) and have used higher order polynomials (cubic polynomials) to capture trajectories

in their studies – suggesting that more assessments of depressive mood within a shorter period of time may require more advanced and complicated models to fully capture the changes across different periods of development (i.e., from childhood to adolescence, changes in adolescence and then from adolescence to young adulthood).

4.5.3 Multiple-subpopulations in ALSPAC

The analysis in this chapter also revealed that a five trajectories solution was preferred in ALSPAC. Previous studies have identified multiple trajectories for this developmental period, with several also identifying five trajectory solutions, similar to what we observed [34, 72, 73]. Within ALSPAC, previous research using the multiple trajectories approach has identified four [75] and three [87] trajectories respectively. The trajectories estimated here are broadly consistent with these studies in that the majority of the population fall into some stable low trajectory. However, there are differences in the number of individuals that fall into some of these intermediary trajectories which results from the number of trajectories identified and then classification of individuals into these trajectories. In both the previous studies, data were only available up to the age of approximately 18. In the latter case, the binary version of the SMFQ was used, rather than the continuous summary score. It is likely that the additional assessments of depressive symptoms that were recently released by ALSPAC allowed me to identify additional trajectories, that were not present in previous studies. Still, it is important to determine whether these trajectories are clinically meaningful or just a product of discrete groups of data. Previous research examining different types of depression within the population has identified four groups of individuals that are somewhat consistent with the trajectories that I and other researchers have identified using the multiple-subpopulation approach [142]. Here Jaffee and colleagues observed that the majority of individuals within the population did not have a diagnosis of depression up until the age of 26 (65% of individuals), whilst 31% of individuals had a diagnosis between the ages of 18 and 26. Likewise, 2% had a diagnosis between the ages of 11 and 15 but not after and 3% had a diagnosis of depression across adolescence and young adulthood. Whilst the prevalence estimates vary for the results presented here and for other studies using ALSPAC data, they give weight to the idea that depression is heterogeneous within the population and characterised by varying timings of onset, severity and chronicity. We were able to identify these profiles with these trajectories analysis and the variation in estimates could be a result of the timing between the studies as adolescent depression is though to be increasing in recent times [21], and that study was conducted in 2002.

4.5.4 Similarities and opposites

The distinction and similarities between these two approaches for deriving trajectories of depressive symptoms is interesting and worth discussing. Both approaches model individual level trajectories, yet the multiple-subpopulation trajectories approach categorises these individuals into multiple discrete distinct groups, whilst the population-averaged approach just takes the average of all the individuals. An interesting question is whether the discrete or continuous trajectories have an overall impact on the interpretation of the results, especially with regards to earlier risk factors. This question is not possible to answer without the inclusion of risk factors into the model. In the conclusions chapter I give an answer this question with regards to several risk factors. However, what is clear that both approaches deal with heterogeneous trajectories differently and that both approaches can be used for examining trajectories of depressive symptoms. Both approaches also suggest that change in depressive symptoms is non-linear and requires advanced modelling to capture these changes across development. We see that in all the trajectories apart from the stable low, there are changes in depressive symptoms that may be characteristic of the nature of depressive symptoms such as the age of onset, chronicity and severity. For example, in the multiple-trajectories approach, the late adolescent onset trajectory may characterise a group of individuals who have an onset of depression during adolescence, which is commonly reported [16]. Something similar is also observed with the population-averaged approach, where depressive symptoms increase at a much higher rate during adolescence.

It may be possible to harmonise both approaches for examining the nature of depressive symptoms. That is to say that both approaches may yield the same answer when it comes to examining what risk factors may be associated with higher trajectories for example. Likewise, they may yield very different answers and interpretations that indicate that both approaches cannot be harmonised. However, it is important to highlight here that the thesis is not concerned with whether one approach is better than the other. Instead this thesis seeks to use both approaches for inferring more about how genetic and environmental contributions to trajectories of depressive symptoms. In the following chapters, I will explore this possibility as I look to see how varying genetic and environmental risk factors may be differentially associated with these trajectories of depressive symptoms. As mentioned in the literature review, one advantage of the multiple-subpopulation approach is that it can handle multivariate analysis better than the population-averaged approach. Therefore, the multiple-subpopulation approach provides the ideal platform for examining the association between both genetic and environmental risk factors and trajectories of depressive symptoms.

4.6 Chapter summary

The aim of this chapter was to derive trajectories of depressive symptoms in ALSPAC using two different methodologies: the population averaged approach (within the multilevel growth-curve modelling framework) and the multiple-subpopulation trajectories approach (within the growth mixture modelling framework). As such, this chapter has addressed the first research objective and I have shown that it was necessary to build upon previous work examining growth curve models within ALSPAC, as the models used in previous studies would not sufficiently model the newly available data in ALSPAC. These trajectories can now be used to address the subsequent research objectives throughout the remainder of this thesis. In the next chapter I take the multiple trajectories derived from the growth mixture modelling approach to examine how genetic and environmental risk factors may be differentially associated with these five differing trajectories in a multivariate approach. In chapters 6,7 and 8 I then expand upon those results (from chapter 5) and use the population averaged approach to examine specific associations between risk factors and trajectories of depressive symptoms.

Chapter 5

Genetic and Environmental Risk Factors Associated with Trajectories of Depressive Symptoms from Adolescence to Young Adulthood

5.1 Chapter outline

This chapter uses the five multiple-subpopulation trajectories identified in the previous chapter to examine the association between genetic and environmental risk factors and trajectories of depressive symptoms across adolescence and young adulthood. As stated in the literature review, this is the more common approach for examining the association between trajectories of depressive symptoms and earlier risk factors - partially due to the ability to include multiple risk factors in a multivariate analysis. Therefore, this chapter explores whether there are differential effects of multiple genetic and environmental risk factors on trajectories. These results could shed light on the aetiology of trajectories of depressive symptoms and guide the timing and focus of prevention strategies. However, the results from this chapter can also be expanded upon and investigated further and in more detail with the population-averaged approach (as done in chapters 6, 7 and 8).

This chapter addresses the second research objective: "how are genetic and environmental risk factors differentially associated with varying trajectories of depressive symptoms?" and provides a platform for subsequent chapters which expand upon this work and address subsequent research objectives. This chapter also contributes

to the existing literature on risk factors associated with trajectories of depressive symptoms and part of this chapter was published as a manuscript in JAMA Network Open as below (additional supplementary materials are provided in appendix 5).

Kwong, A. S. F., Lopéz-Lopéz, J., Hammerton, G., Manley, D., Timpson, N. J., Leckie, G., Pearson, R. M. (2019). Genetic and Environmental Risk Factors Associated with Trajectories of Depressive Symptoms from Adolescence to Young Adulthood. JAMA Network Open. 2, doi:10.1001/jamanetworkopen.2019.6587

5.2 Chapter abstract

Less favourable trajectories of depressive mood across adolescence into early adulthood are associated with current and later psychopathology, impaired educational attainment and social dysfunction, yet the genetic and environmental risk factors associated with these trajectories are not fully established. Examining what risk factors are associated with different trajectories of depressive mood could help identify the nature of depressive symptoms and improve preventative interventions for those at most risk.

To examine how genetic and environmental risk factors differentially associate with trajectories of depressive symptoms between ages 10 to 24 years.

In a longitudinal cohort study established in 1990 and currently ongoing (Avon Longitudinal Study of Parents and Children), I used growth mixture modelling to identify trajectories of depressive symptoms in 9,394 individuals. I then examined associations between different risk factors and membership in these trajectories. Analysis was conducted between August 2018 and January 2019.

Trajectories were composed from depressive symptoms measured using the short mood and feelings questionnaire (SMFQ) across nine occasions between the ages 10 and 24 years. Risk factors included sex, a polygenic risk score (PRS) taken from a recent genome wide association study of depressive symptoms, maternal postnatal depression, partner cruelty to the offspring's mother between ages 2-4 years, childhood anxiety at age 8, being bullied at age 10.

Data on all risk factors, confounders and the outcome were available for 3,525 individuals, including 1,771 (50.2%) females. Trajectories were assessed between 10.65 years and 23.8 years. I identified 5 distinct trajectories of depressive symptoms: 'stable low' (71.1%), 'adolescent limited' (9.2%), 'childhood limited' (5.8%), 'early-adult onset' (11.1%) and 'childhood persistent' (2.8%). Of all the associations between risk factors and trajectories, female sex (OR, 6.45; 95% CI, 2.89-14.38), the

PRS for depressive symptoms (OR, 1.47; 95% CI, 1.1-1.96) and childhood anxiety (OR, 1.3; 95% CI, 1.16-1.45) showed strongest associations with the childhood persistent trajectory, compared to the stable low trajectory. Maternal postnatal depression (OR, 2.39; 95% CI, 1.41-4.07) had the strongest association with the early-adult onset trajectory, whilst partner cruelty to mother (OR, 2.3; 95% CI, 1.36-3.9) had the strongest association with the adolescent limited trajectory. Bullying (OR, 8.08; 95% CI, 4.92-13.26) showed the strongest association with the childhood limited trajectory.

The least favourable trajectories of depressive symptoms (childhood persistent and early-adult onset) were associated with both genetic and environmental risk factors. However, the two trajectories of limited duration that had resolved by early adulthood (childhood limited and adolescent limited) were not associated with the PRS or maternal postnatal depression (two more 'genetic' risk factors). Instead, bullying (a more 'environmental' exposure) was strongly associated with both the childhood onset and childhood limited trajectories, suggesting that this risk factor may have a time-specific impact. These findings suggest that examining genetic and multiple time-specific environmental antecedents could help identify trajectories of varying onset and chronicity. Understanding whether there are different risk profiles (including timing/nature of exposure and prior vulnerabilities) may offer more opportunities to target interventions at certain stages of development.

5.3 Introduction

As stated in the introduction, Depression is a leading cause of disability worldwide [2], expected to be the highest global burden of disease by 2030 [3]. Despite efforts to improve interventions, prevalence is still increasing, especially in adolescence [21]. Evidence suggests that depression during adolescence is associated with many concurrent and later psychological and social impairments [16, 20]. However, what is driving this rise in adolescent depression is still not clear. A greater understanding of the nature of adolescent depression and how to minimise it is crucial if we are to reduce this global burden.

There is evidence that depression should be viewed on a continuum [8, 9], as individuals with subthreshold depression [143, 144] and elevated levels of depressive symptoms [10] are also at risk of concurrent and later psychopathology. Importantly, a similar pattern is also observed for those displaying consistently higher levels of depressive symptoms over time [32, 43, 64, 67, 130]. Detailed longitudinal analysis provides an opportunity to further understand how depression may mani-

fest differentially over time, and its aetiology. Towards this goal, researchers have identified trajectories of depressive symptoms across adolescence and potential risk factors [30, 31]. Previous research suggests that adolescence, is characterised by a clear rise in symptoms of depressed mood, however trajectories vary within the population and differ by age of onset, duration and severity of symptoms [30–32, 103] . Evidence has shown that several less favourable trajectories of depressive symptoms exist (i.e., those with depressive symptoms that start high and continue [childhood persistent], those that start low but rise over time [early-adult onset] or those that that start high in early childhood but decline over adolescence and young adulthood [childhood limited]), which are present across multiple populations and all often associated with poorer outcomes compared to the majority of adolescents with low symptoms over time (stable low) [32, 34, 37, 43]. It may be possible to start targeting specific interventions and treatments for certain individuals by disentangling different risk factors (or different combinations of risk factors) for different trajectories.

Identifying how different risk factors are associated with varying patterns of depressive mood could be important for understanding the aetiology of depression and improving treatment. Risk factors such as being female [37, 64], childhood psychopathology [34, 43], parental mood [36, 37] and early life socioeconomic position [43, 145] are important predictors of less favourable trajectories of depressive symptoms. Stronger associations are typically observed for chronically high or rising trajectories (Costello et al., 2008; Ferro et al., 2015; Stoolmiller et al., 2005; Weeks et al., 2014; Yaroslavsky et al., 2013) [34, 36, 37, 43, 103], yet the evidence for this is not clear cut. A recent study also found that polygenic risk for depression was associated with a late adolescent onset trajectory [87], implying genetic liability may be a key component for higher trajectories at specific periods of development [146]. The evidence is less clear on what predicts more adolescent or childhood limited trajectories, although research suggests they could be reactive to more immediate stressors and events [43]. For example, bullying is arguably one of the strongest predictors of adolescent and adulthood depression [25, 147, 148], and is most frequent and salient during certain periods of childhood and adolescent development. Therefore, bullying in childhood is likely to have immediate consequences. However, the direction of this association is unknown and there is evidence that as bullying is also associated with depression across the life-course suggesting it could also be reflective of pre-existing vulnerability [149]. Therefore, it is unclear whether the relationship between bullying and depression is time-specific and/or dependent on other prior vulnerabilities [150]. Investigating how bullying affects differential trajectories of depressive symptoms across adolescent development could give insight into how and when the impact of this key risk factor occurs. Bullying in childhood has also yet

to be linked to different trajectories of depressive symptoms.

Trajectories of depressive symptoms are likely to have a highly complex aetiology comprised of both genetic and environmental influences. This is because behavioural phenotypes such as depression are unlikely to have purely direct genetic or environmental pathways [27]. Instead, it is more likely that an interplay of gene-environment correlations exists and that complex traits (such as depression) may have a greater contribution of genetic or environmental contributions [9, 87, 148, 151, 152]. For example, stressful life events may cause higher depressive symptoms, but it is possible that genetically liable individuals may be more prone to stressful life events, thus making it hard to determine the direction of effects. Therefore, whilst we cannot yet separate whether a risk factors operates through genetic or environmental mechanisms, examining both genetic and environmental risk factors could build better prediction models and provide new understanding which could be translated into improved prevention and interventions.

Currently, no studies have examined the longitudinal nature of trajectories of depressive symptoms across adolescence and associations with both genetic and environmental risk factors between early childhood and adolescence. Understanding whether different risk profiles are associated with specific manifestations of trajectories of depressive symptoms may offer more precise opportunities to target interventions during certain periods. I hypothesized that the most vulnerable trajectories (i.e., childhood persistent) would be associated with a combination of both genetic and environmental risk factors (possibly reflecting a complex gene-environmental interplay, and/or greater genetic contribution where genetic liability is reinforced by environmental events). However, given the ambiguity surrounding the antecedents of adolescent or childhood limited trajectories, there may be some specificity in these trajectories that could be more reflective of emotional reactions to recent negative environmental events, such as bullying.

5.4 Methods

5.4.1 Sample

As described in chapter 3, data were from the Avon Longitudinal Study of parents and Children (ALSPAC).

5.4.2 Depressive symptoms

Self-reported depressive symptoms were measured on nine occasions between ages 10 and 24 using the short mood and feelings questionnaire (SMFQ) [129], as described in chapter 3. Further descriptive information for this chapter can be found in appendix 5.

5.4.3 Risk factors

Biological Sex was identified from birth notifications taken around the time of delivery and was coded as male or female. Data for four individuals were missing.

As mentioned in the literature review, it is possible to estimate an individuals genetic liability to a trait (such as depression) through the use of polygenic risk scores (PRS) [29]. Polygenic risk scores are created from summary statistics taken from large scale genome-wide association studies (GWAS). GWAS look to identify specific genetic variants (or single nucleotide polymorphisms [snps]) that are robustly associated with a trait [9]. PRS are usually weighted by their effect size (taken from the intial GWAS) and the number of risk alleles that an individual possesses [153], and at their most basic can be thought of as summary score of an individuals liability to a disease or trait. In the context of depressive symptoms and this thesis, a PRS can be used to explore the association between genetic liability for depressive symptoms and measured depressive symptoms in later life. PRS are not subject to usual confounding as these snps are fixed at birth and cannot change. However, just because these snps are fixed, does not necessarily mean they cause depression or other traits. They essentially assess an individuals liability to depression and as discussed earlier, depression is likely to be based upon a complex gene-environment correlation. Finally, these PRS can be used for exploring associations but liberal PRS (that have multiple risk variants) should not be used as instruments for methods like Mendelian randomization due to violations in assumptions like pleitropy (one gene affecting multiple traits) [154].

The PRS used here was a PRS for depressive symptoms was created in PRSice [155], using summary statistics from a recent GWAS of depressive symptoms on 161,460 individuals [156]. I included SNPs that had a MAF of $> 1\%$ and info score $> 80\%$) and excluded SNPs with an R2 of >0.1, which were within 250Kb of each other. I excluded SNPs located in the extended MHC region (chromosome 6 (26-33Mb)). Participant genotyping information is available in appendix 5. The PRS was created by weighting the effect sizes of 120,422 single nucleotide polymorphisms (SNPs) associated with depressive symptoms from the initial GWAS at eight p-value

thresholds (between 5x10-8 and 0.5; see appendix 5 for further details) and I used the most liberal threshold (0.5) for prediction based upon recent evidence that more liberal polygenic scores may be better predictors if the scores are only concerned with maximising prediction [9, 122]. The PRS was standardised to have a mean of 0 and a standard deviation of 1, thus a higher PRS represents higher liability to depressive symptoms but this should be normally distributed across the population (see Figure 5.1. for a distribution of the PRS). Population stratification can be a problem in genomic analysis, so to account for this I adjusted this analysis for the first five principal components of ancestry, as per previous studies [157].

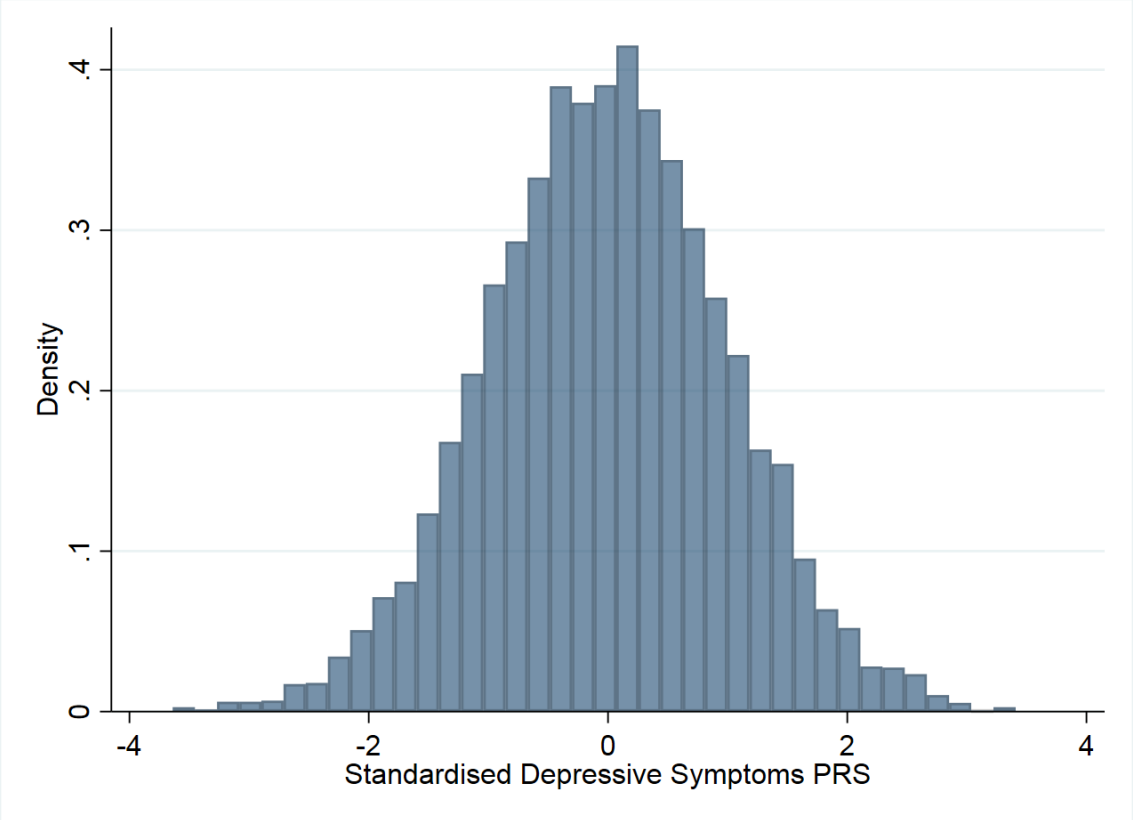


Figure 5.1: Histogram of the depressive symptoms polygenic risk score

Postnatal Depression was assessed at 8 weeks postpartum by the mother completing the Edinburgh Postnatal Depression Scale (EPDS) [158]. A cut-off score of 13 or more indicating probable depression was used [159, 160]. Postnatal depression was chosen given the high correlation between pre and post-natal depression [161].

Cruelty to the Mother was assessed by the Family Adversity Index (FAI) which asked the mother whether her partner was abusive towards her between the child's ages of 2-4 years (yes vs no) [145].

Childhood Anxiety was measured at approximately age 8 by asking the child's main caregiver about the child's general anxieties taken from the Development and Well-Being Assessment (DAWBA) [162]. A weighted summary score between 0-12 was

created from 6 questions on childhood anxiety, with 12 indicating maximum childhood anxiety. These scores were derived from the following questions where the response could be not at all; yes, but not on most days or yes, more days than not:

1. Does worrying lead to her/him being restless, feeling keyed up, tense or on edge, or being unable to relax?
2. Does worrying lead to her/him feeling tired or "worn out" more easily?
3. Does worrying lead to difficulties in concentrating or her/him mind going blank?
4. Does worrying lead to irritability?
5. Does worrying lead to her/him looking physically tense (tense muscles)?
6. Does worrying interfere with her/him sleep (e.g. difficulty in falling or staying asleep, or restless sleep, or doesn't have a good night's sleep)?

Childhood Bullying was measured at approximately age 10 when the child attended a research clinic, using the modified Bullying and Friendship Interview Schedule [163]. A child was classed as being bullied, if he/she was on the receiving end of any of the following five components of overt bullying frequently (several times a month) or very frequently (several times a week):

1. Had personal belongings taken
2. Been threatened/blackmailed
3. Been hit/beaten up
4. Been tricked in a nasty way
5. Been called bad/nasty names

I used a binary variable to assess bullying of the child in the last 6 months (yes vs no).

5.4.4 Confounders

The following confounders were included based upon previous literature linking them to the risk factors and the depressive trajectories but not under current investigation as hypothesised primary risk factors [75, 115, 160]: maternal age at birth (in years),

maternal occupational status at birth (manual vs non-manual), maternal educational attainment at birth and parity (1st born vs 2nd born vs 3rd born or more) and the first 5 principle components of ancestry to control for population stratification in the genetic analysis. These were included to examine the impact of confounders on the relationship between depressive symptoms and the risk factors, as well as being markers of missing data and participant demographics.

5.4.5 Statistical analysis - growth mixture modelling

I conducted growth mixture modelling (GMM) in Mplus version 8 [139] to identify latent trajectories of depressive symptoms as described in the previous chapter. Briefly, GMM stratifies individuals from a population into multiple heterogeneous trajectories (or latent classes) [40]. Odds ratios (ORs) and their corresponding 95% confidence intervals (95% CI) were derived from multinomial logistic regressions, where the trajectory with the largest sample size was used as the reference. Further details about model fit and how I assessed the validity of these trajectories can be found in chapter 4 and appendix 5.

5.4.6 Missing data

Missing data in the GMM were handled using full information maximum likelihood estimation (FIML) [139]. I included individuals into this analysis if they had at least one measurement of depressive symptoms [87]. Previous research on this data has demonstrated little difference on the shape of trajectories, distribution of trajectory membership and associations between trajectories and outcomes when comparing individuals with at least one measurement of depressive symptoms to participants with at least 3, or all 9 measurements [130].

5.5 Results

Data were available for 9,394 individuals with at least 1 measurement of depressive symptoms. Demographics for these individuals can be found in appendix 5, but briefly, individuals included in the analysis were more likely to be female and have mothers with better education and occupational status at birth. The sample size for individuals with all risk factors and confounders was 3,525, including 1,771 (50.2%) females. The mean age at the first occasion of depressive symptoms was 10.65 years and 23.8 years at the last assessed occasion. Results from the GMM indicated a 5-class trajectory solution best suited the data (as described in chapter 4). The shapes

of these trajectories and class distributions did not differ substantially between the sample consisting of 9,394 and the sample of 3,525 (see appendix 5). The following analysis uses this sample of 3,525.

5.5.1 Trajectories of depressive symptoms

5 heterogeneous trajectories of depressive symptoms were derived: individuals who had consistently low levels of depressive symptoms - stable low (71.1%), individuals who started with low depressive symptoms but rose throughout adolescence and young adulthood – early-adult onset (11.1%), individuals who experienced elevated levels of depressive symptoms only during adolescence – adolescent limited (9.2%), individuals who started with elevated levels of depressive symptoms in childhood which decreased over time – childhood limited (5.8%) and individuals with moderate levels of depressive symptoms that continued to rise and stay high across adolescence and into young adulthood – childhood persistent (2.8%), see figure 5.2 (reproduced from chapter 4 for ease of readership).

5.5.2 Association between risk factors and trajectories of depressive symptoms

Unadjusted and adjusted results from the multivariate analysis between risk factors and varying trajectories are presented in tables 5.1 and 5.2. The risk factors for varying trajectories of depressive symptoms are shown in figure 5.3. For all the following analysis, the odds ratio (OR) is for each trajectory compared to the stable low. Correlations between risk factors and univariate or unadjusted multivariate analyses are given in appendix 5.

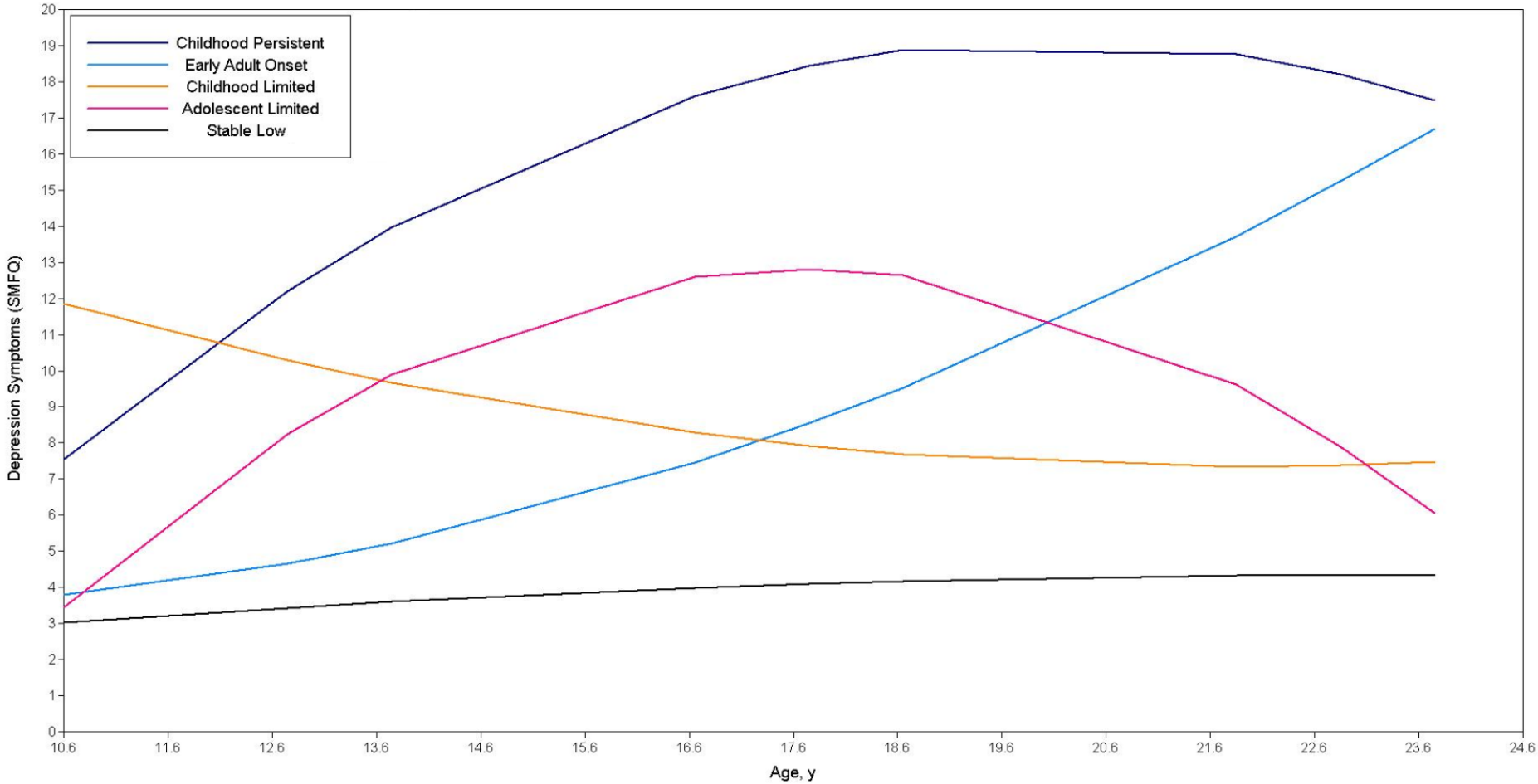


Figure 5.2: 5 trajectories from the growth mixture modelling in ALSPAC used in this chapter. Note this graph is recycled from the previous chapter.

	Multinomial Odds Ratios (ORs) [Lower, Upper 95% CIs]				
	Childhood persistent vs. Stable low	**Early-adult onset vs. Stable low**	**Adolescent limited vs. Stable low**	**Childhood-limited vs. Stable low**	**Omnibus *p*-value**
Sex					
Female	6.09 [2.91, 12.74]	2.22 [1.55, 3.19]	5.9 [3.6, 9.66]	1.88 [1.23, 2.89]	<.001
Genetics					
Polygenic Risk Score	1.54 [1.16, 2.02]	1.28 [1.08, 1.52]	1.12 [0.93, 1.35]	1.05 [0.86, 1.29]	0.002
Early Life					
Postnatal Depression	2.56 [1.3, 5.02]	1.98 [1.2, 3.28]	1.18 [0.64, 2.2]	1.69 [0.9, 3.18]	0.009
Cruelty to Mother 2-4 Years	1.82 [0.82, 4.05]	2.17 [1.36, 3.46]	2.13 [1.33, 3.42]	1.07 [0.54, 2.12]	0.001
Childhood					
Anxiety at 7.6 Years	1.26 [1.12, 1.4]	1.12 [1.02, 1.23]	1.1 [1.0, 1.21]	1.27 [1.14, 1.41]	<.001
Bullied at 10 Years	4.23 [2.27, 7.89]	1.71 [1.12, 2.6]	1.37 [0.84, 2.25]	7.55 [4.86, 11.71]	<.001

Table 5.1: Unadjusted multivariate associations between genetic and environmental risk factors and trajectories of depressive symptoms. Note: Analysis was adjusted for all risk factors.

	Multinomial Odds Ratios (ORs) [Lower, Upper 95% CIs]				
	Childhood persistent vs. Stable low	**Early-adult onset vs. Stable low**	**Adolescent limited vs. Stable low**	**Childhood-limited vs. Stable low**	**Omnibus *p*-value**
Sex					
Female	6.45 [2.89, 14.38]	1.96 [1.33, 2.88]	6.04 [3.35, 10.87]	1.81 [1.13, 2.9]	<.001
Genetics					
Polygenic Risk Score	1.47 [1.1, 1.96]	1.29 [1.06, 1.57]	1.04 [0.85, 1.27]	1.01 [0.81, 1.25]	0.012
Early Life					
Postnatal Depression	2.37 [1.16, 4.85]	2.39 [1.41, 4.07]	1.12 [0.54, 2.31]	1.7 [0.8, 3.62]	0.005
Cruelty to Mother 2-4 Years	1.61 [0.66, 3.95]	1.78 [1.05, 3.04]	2.3 [1.36, 3.9]	1.06 [0.48, 2.37]	0.008
Childhood					
Anxiety at 7.6 Years	1.3 [1.16, 1.45]	1.12 [1.01, 1.24]	1.09 [0.98, 1.21]	1.23 [1.08, 1.41]	<.001
Bullied at 10 Years	4.91 [2.52, 9.58]	1.73 [1.1, 2.7]	1.56 [1.0, 2.44]	8.08 [4.92, 13.26]	<.001

Table 5.2: Adjusted associations between genetic and environmental risk factors and trajectories of depressive symptoms. Note: Analysis was adjusted for all risk factors and the following confounders: maternal age at birth, maternal occupational status at birth, maternal educational attainment at birth and parity.

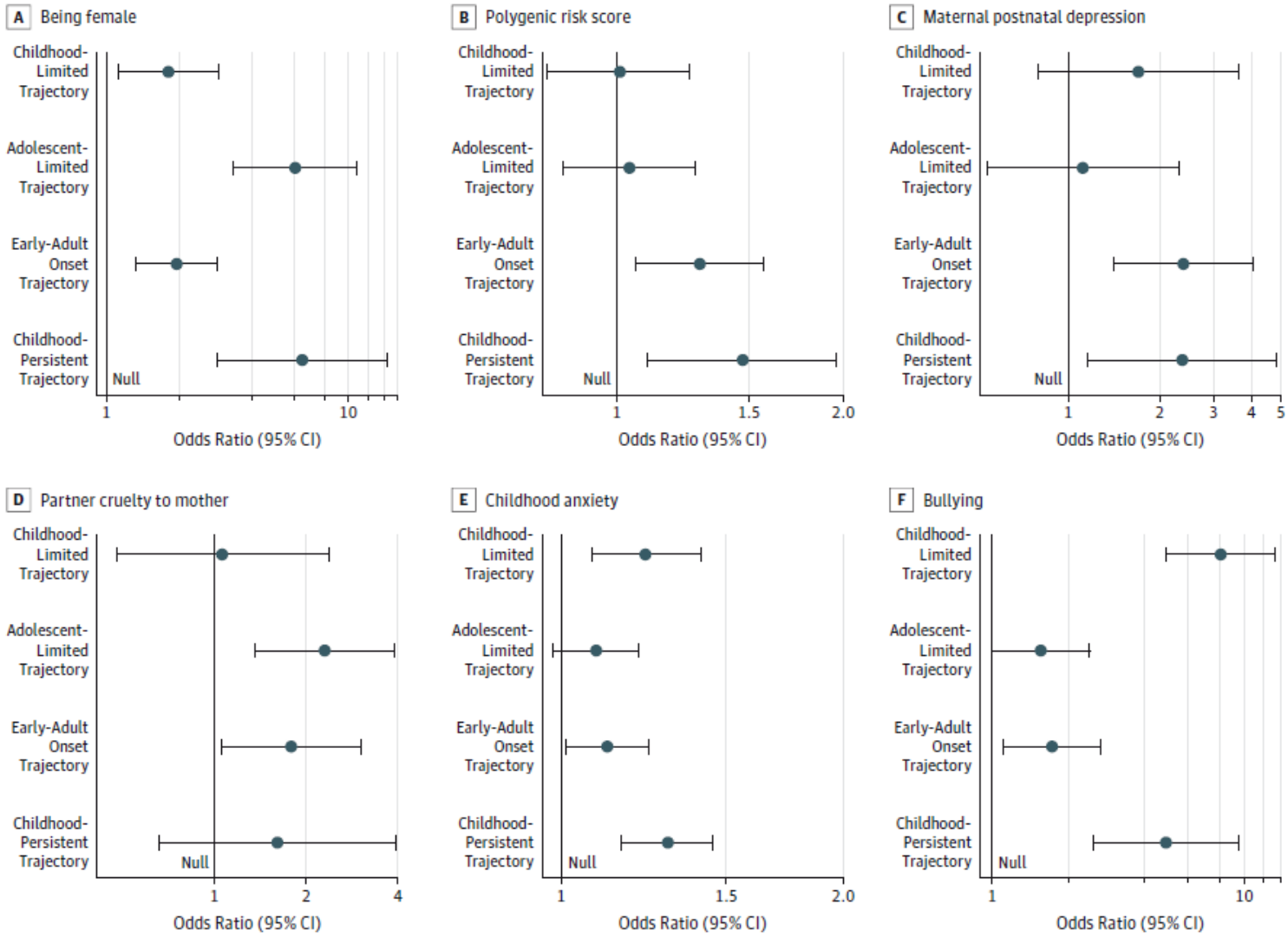


Figure 5.3: Association between (A) being female, (B) polygenic risk, (C) maternal postnatal depression, (D) partner cruelty to mother, (E) childhood anxiety and (F) bullying and trajectories of depressive symptoms.

5.6 Discussion

I used the five distinct trajectories of depressive symptoms established in chapter 4. These trajectories were associated with both genetic and environmental risk factors. These findings suggest that examining both genetic and environmental antecedents could help identify groups with severe and chronic depressive symptoms (childhood persistent), who should be prioritised for early intervention. Certain risk profiles also show specific associations with longitudinal patterns of depressive symptoms.

Polygenic risk for depressive symptoms (i.e., greater genetic liability to depression) was associated with the childhood persistent and early-adult onset trajectories, which supports the notion that genetic liability may play an important role in the onset of depression in adolescence [87, 142]. Polygenic risk has previously been associated with both depression and higher trajectories of depressive symptoms in later adult populations [164, 165]. However, these results suggest that genetic liability to greater depressive symptoms may begin to manifest in both childhood and adolescence, highlighted in previous research [87]. As such, genetic liability could be a mechanism for chronic and/or higher depressive symptoms across the life-course, that operates through specific neurological or hormonal systems at certain stages of development [146]. Similar results have been observed for trajectories of attention-deficit/hyperactivity disorder (ADHD) [166], suggesting that genetic liability can impact on the development of a trait. However, it is unlikely that genetic liability alone is responsible for higher trajectories. Instead, a more plausible explanation is that a complex interplay between genetics and the environment exists [27, 142, 151]. However, this is not yet understood and it is also not clear how genetic liability of depression might impact on later environmental risk factors [167]. Future research should look to explore this in order to discover potential pathways and mechanisms involved in the maintenance of depression.

Previous research has shown that bullying is highly predictive of the onset of depression in adolescence and adulthood [25, 147], however these findings highlight that being bullied in childhood is strongly associated with both short and long-term consequences. Whether exposure to bullying has a lasting impact may depend on genetic vulnerabilities in both depression and vulnerability to bullying [148–150]. Bullying was assessed at age 10 (shortly before the first assessment of depressive symptoms) and was most strongly associated with the childhood-limited trajectory that showed high symptoms in early childhood that diminished over time. This could reflect an immediate reaction to bullying which then resolves, thus making bullying time-specific as bullying had weaker associations with the early-adult onset and adolescent limited trajectories. However, bullying was strongly associated with the

childhood persistent trajectory, suggesting there could be long term consequences for individuals who were bullied in childhood (but still have consistently high symptoms over 10 years later). The difference between these two resulting trajectories could be that the childhood persistent group also have genetic and additional environmental vulnerabilities that make it harder to recover. This supports previous research highlighting genetic liability to schizophrenia and subsequent bullying is associated with worse trajectories of poorer mental health [168]. This suggests that victims of bullying that also have family and accumulating risks should be prioritised for intervention. A similar interpretation could exist for childhood anxiety, which showed associations with the childhood persistent, early-adult onset and childhood-limited trajectories. Interventions to build resilience early on for those with genetic liability may yield the most effective method for prevention of long-term or severe depression.

Sex differences have consistently been associated with less favourable trajectories of depressive symptoms [99] and we observe strong associations between females and the childhood persistent rising and adolescent limited trajectories, supporting previous research [37]. The childhood persistent and adolescent limited trajectories are distinct, yet the reason why we observed these differences may also be due to childhood persistent rising females having a genetic liability to depression in addition to other factors such as early pubertal timing [99, 133] and stress reactivity [105]. In contrast, the adolescent limited females who may not have the genetic liability to depressive symptoms are maybe reacting only to early pubertal timing or stressful events. However, it is likely that other biological and environmental risk factors underlie less favourable trajectories for females, and more research is needed to disentangle this relationship.

Maternal postnatal depression was associated with the childhood persistent and early-adult onset trajectories, likely reflecting the transmission of maternal depression to offspring depression [23, 159, 169, 170]. This association likely reflects genetic influences (as these two trajectories were associated with the PRS) as well as possibly impacting parental depression on offspring brain development in utero [23, 171]. Alternatively, it could reflect childhood vulnerabilities established in infancy and early development that results in later depression [169]. As postnatal depression was not associated with the adolescent limited or childhood-limited trajectories (i.e., trajectories not associated with genetic liability), it may suggest that maternal depression has more long-lasting associations possibly through a genetic and environmental interplay. Interestingly, this pattern was not observed for partner cruelty to the mother, which was associated with the early-adult onset and adolescent limited trajectories, but not the childhood persistent or childhood limited trajectories

(the trajectories associated with bullying). It could be that partner cruelty operates through a different pathway and does not share the same time-specific impact compared to bullying. Instead, membership into the adolescent limited trajectory could be reflective of depressive symptoms that reduce post adolescence once they are less influenced by family life. However, partner cruelty to the mother is a rare exposure and it is possible that the associations between the early-adult onset and adolescent limited trajectories may reflect a lack of power, rather than a true association.

5.6.1 Strengths and limitations

Previous research has validated the five-class trajectory model by observing that different trajectories correspond with a diagnosis of depression that is applicable to each time (i.e., childhood limited had a stronger association with a diagnosis early on; early-adult onset had a stronger association with depression at a later diagnosis) [130]. Five-class trajectories have also been observed in other longitudinal cohorts using similar methods, thus increasing the generalisability of these trajectories [72, 73]. However, it is worth noting that previous research using the same data (albeit only to age 18) only identified three trajectories of depressive symptoms, compared to the five in the present analysis [87]. This is likely a result of the additional three measurement occasions and that I used a continuous scale of depressive symptoms, compared to the binary diagnosis used by Rice and colleagues. Despite these methodological differences, these results were broadly the same as genetic liability to depressive was associated with a later onset trajectory, and weakly associated with an early onset trajectory. Additionally, I used both genetic and environmental risk factors with greater longitudinal data on depressive symptoms to explore the long-term impact of these risk factors. However, one of the problems with longitudinal cohort studies relates to attrition and although the model utilised full information maximum likelihood to account for missing data, the data could be missing not at random potentially leading to biased results. Furthermore, the interplay between genetics and the environment is highly complex as genetic and environmental risk factors are not independent (highlighted by previous research and correlations between genetic and environmental risk factors in appendix 5). It is therefore hard to disentangle genetic liability from later environmental risk factors that could be on the causal pathway. The analysis using genetic data was also restricted to non-related individuals and individuals of European descent. Previous research has shown ethnic differences in trajectories of depressive symptoms, with Black, Asian and Hispanic populations all showing less favourable trajectories of depression [88, 97]. I was unable to explore trajectories in these populations due to the availability of DNA samples from the depressive symptoms GWAS and exclu-

sion criteria, thus these results lack generalisability to these populations. However, GWAS are being applied to other non-European populations and so future work will be able to untangle ethnic differences in depression research using genetic and environmental determinants [121]. It is also important to note that I made multiple comparisons and confidence intervals in many cases overlapped and therefore the specificity of the associations deserves replication. Future research that also untangles genetic-environment correlations will be pivotal for identifying pathways and mechanisms underlying various forms of depression. This will eventually lead to the improvement and treatment of depression.

5.7 Conclusions

I used five trajectories of depressive symptoms between late childhood and young adulthood. The childhood persistent and early-adult onset trajectories were associated with genetic and environmental risk factors. These findings suggest that looking at the combination of both genetic and environmental antecedents could help identify groups with chronic and severe depressive symptoms, who should be prioritised for intervention. Yet the severity and course of these symptoms could depend on the timing of specific risk factors and other prior vulnerabilities. For example, bullying was strongly associated with both the childhood onset and childhood limited trajectories, suggesting it may be time-specific and that severity and duration could depend on other vulnerabilities (i.e., genetic liability). Overall, these findings imply that the aetiology for different trajectories of depressive symptoms is multifactorial, with a complex interplay of genetic and environmental contributions. It may be possible to differentiate between different risk profiles that show varying trajectories of depressive symptoms. This could be transformed into the development of interventions and treatments for those at most risk of greater depressive symptoms, which could in turn prevent or reduce depression and other detriments in later life.

5.8 Chapter summary

This chapter has shown that certain genetic and environmental risk factors may be differentially associated with varying trajectories of depressive symptoms and in doing so has addressed the second research objective "how are genetic and environmental risk factors differentially associated with varying trajectories of depressive symptoms?". The findings presented here are the first to combine both polygenic

risk and environmental risk factors within the same model and have contributed to the existing literature. However, this is only one approach to examining trajectories of depressive symptoms and as stated in the literature review (chapter 2), an alternative approach can be used to derive population-averaged approaches for examining associations between risk factors and trajectories of depressive symptoms. In chapters 6, 7 and 8, I build upon this chapter to examine in more detail how several of the genetic and environmental risk factors identified here are associated with population averaged trajectories. Using both approaches will provide a dual prospective on how genetic and environmental risk factors might play a role in the longitudinal nature of depressive symptoms.

Chapter 6

Sex Differences and Trajectories of Depressive Symptoms from Childhood to Young Adulthood

6.1 Chapter outline

This chapter follows on from the conclusions of the last chapter (chapter 5) and from existing research highlighted in the literature review (chapter 2): that female sex is a strong risk factor for higher trajectories of depressive symptoms. In the previous chapter using a multivariate analysis, I showed that female sex was strongly associated with the four "higher" trajectories, compared to the stable-low trajectory. However, these results can be expanded to explore when female sex is having the greatest effect on these trajectories. Therefore, the aim of this chapter was to explore this association in more detail using the population-averaged approach for estimating trajectories of depressive symptoms. In chapter 4, I derived the population-averaged trajectories using multilevel growth curve models and in this chapter I use this model to compare trajectories of depressive symptoms between females and males in a more holistic approach that characterises the nature of depressive mood for each sex across multiple stages of development[1]. With this chapter I also wanted to build upon previous growth curve model research by estimating critical points in these trajectories such as the age of peak velocity (i.e., the age at which depressive symptoms are increasing at the fastest rate) or age at maximum depressive symptoms, which could be useful a tool for examining important points at which it may be beneficial to intervene to reduce current or later depressive

[1]Note: this chapter was conducted before the release of the ninth SMFQ data wave, and so this chapter focuses on only the first 8 waves of the SMFQ and was modelled with a cubic polynomial model - see appendix 6.

symptoms.

This chapter addresses the second research objective: "how are genetic and environmental risk factors differentially associated with varying trajectories of depressive symptoms?" but also the third research objective: "are there critical points in trajectories of depressive symptoms which tell us more about how and when depression changes across adolescence?" and the fourth research objective: "can the results from trajectory models be simplified to aid in the interpretation and translation of findings?". As such, this chapter advances the findings from the previous chapter by highlighting different ages at which depressive symptoms could be getting worse or when they are at their worst and how this varies by sex. Part of this chapter was published as a manuscript in the Journal of Youth and Adolescence as below (with supplementary materials provided in appendix 6).

Kwong, A. S. F., Manley, D., Timpson, N. J., Pearson, R. M., Heron, J., Sallis, H., Stergiakouli, E., Davis, O., Leckie, G. (2019). Identifying Critical Points of Trajectories of Depressive Symptoms from Childhood to Young Adulthood. Journal of Youth and Adolescence. 48, 815-827. doi.org/10.1007/s10964-018-0976-5

6.2 Chapter abstract

Research has focused on late childhood and adolescent depression in an attempt to prevent or reduce later psychopathology and/or social impairments. It is important to establish and study population-averaged trajectories of depressive symptoms across adolescence as this could characterise specific changes in populations and help identify critical points to intervene with treatment. Multilevel growth-curve models were used to explore adolescent trajectories of depressive symptoms in 9,301individuals (57% female) from the Avon Longitudinal Study of Parents and Children, a UK based pregnancy cohort. Trajectories of depressive symptoms were constructed for males and females using the short mood and feelings questionnaire over 8 occasions, between 10 and 22 years old. Critical points in development such as age of peak velocity for depressive symptoms (the age at which depressive symptoms increase most rapidly) and the age of maximum depressive symptoms were also derived. The results suggested that from similar initial levels of depressive symptoms at age 11, females on average experienced steeper increases in depressive symptoms than males over their teenage and adolescent years until around the age of 20 when levels of depressive symptoms plateaued and started to decrease for both sexes. Females on average also had an earlier age of peak velocity of depressive symptoms that occurred at 13.5 years, compared to males who on average had an age of peak velocity

at 16 years old. Evidence was less clear for a difference between the ages of maximum depressive symptoms which were on average 19.6 years for females and 20.4 for males. Identifying critical periods for different population subgroups may provide useful knowledge for treating and preventing depression and could be tailored to be time specific for certain groups. Possible explanations and recommendations are discussed.

6.3 Introduction

Research has focused on childhood and adolescent depressive symptoms as a potentially modifiable risk factor for more severe depression during adulthood [10, 32] and previous research has shown that elevated levels of depressive symptoms within a population (and even those that never rise above the threshold for depression) are associated with a greater risk for depression in later life [35, 43]. Evidence concludes that the period between late childhood and adolescence may be important for subsequent mental health and social functioning, thus identifying and treating elevated depressive symptoms during this time could limit or prevent depression in later life through support and services [16, 144].

Research has yet to fully understand the nature of trajectories of depressive symptoms across adolescence and into young adulthood and identifying the key characteristics and time course of depressive symptoms across this period will ultimately aid in improving treatments and interventions. The chapter attempts to build upon previous research by estimating trajectories of depressive symptoms between late childhood and young adulthood, and identifying critical points along those trajectories that could shed light on the nature of how these trajectories of depressive symptoms develop and change over time.

Previous studies have examined trajectories of depressive symptoms between childhood and young adulthood in an attempt to explore the nature and risk factors underlying greater depressive symptoms (see chapter 2), for reviews see Musliner et al. [32], Shore, Toumbourou, Lewis, and Kremer [31] and Schubert, Clark, Van, Collinson, and Baune [30]. Indeed, research suggests that trajectories of depressive symptoms tend to increase from childhood through adolescence, before decreasing in young adulthood [98, 99]. Evidence also suggests that these trajectories may peak in mid-to-late adolescence, towards the ages of 15-17 years old [37, 103].

Other research has suggested that depressive symptoms may increase post adolescence. For instance, Ge and colleagues demonstrated that trajectories of depressive symptoms were highest around the ages of 17 to 18 years old, but were unable

to explore depressive symptoms further than this age due to a cease in data collection [93]. Other research has suggested that trajectories of depressive symptoms are highest in young adulthood (towards age of 20) but then decline until older age [172]. In this instance, Sutin and colleagues did not have data preceding young adulthood so they were unable to explore if trajectories were higher around adolescence. It may be that trajectories of depressive symptoms could peak outside adolescence, yet do not have preceding and succeeding data around this period to substantiate these claims [62, 96]. Likewise, many studies also use small sample sizes, which can make it difficult to infer about population level changes of depressive symptoms.

Observing the longitudinal nature of trajectories of depressive symptoms enables researchers to identify critical points at which to intervene to limit or prevent more severe depression. The notion of identifying critical points is not new [173], but this application to trajectories of depressive symptoms has yet to be fully explored. Using depressive symptoms data from childhood to young adulthood (12 to 25 years), Ferro and colleagues identified the age of maximum depressive symptoms to occur between the ages of 15 to 17 years old [103], whilst Rawana and Morgan found that depressive symptoms were highest at approximately 17 years old [102]. Similar results have also been observed by Natsuaki and colleagues who plotted trajectories that indicated the age of maximum depressive symptoms was 16 years old [99]. Other research has also found evidence of sex differences in regards to an age of maximum depressive symptoms with females reaching this maximum earlier than males [97, 108].

While identifying the age of maximum depressive symptoms is important for characterising the nature of depressive symptoms, calculation of the age of peak velocity may also be important (i.e., the age at which depressive symptoms are increasing most rapidly). Research has suggested that identifying depressive symptoms early or before depression already manifested may be a key step towards preventing greater depressive symptoms or severe depression from occurring [17, 174]. By identifying the age of peak velocity of depressive symptoms, it may be possible to highlight a critical point where interventions and treatments could be implemented to reduce or limit greater depressive symptoms from escalating. However, no studies have calculated the age of peak velocity of depressive symptoms and studies that have previously identified the age of maximum depressive symptoms have done so using heuristics, graphs or figures rather than empirically calculating these ages.

Trajectories of depressive symptoms are not homogeneous within the population [32], and a number of risk factors can influence trajectories of depressive symptoms [43, 175]. Consistent evidence has shown that females tend to have higher trajectories of depressive symptoms compared to males [43, 64]. Although in several studies

where heterogeneous trajectories are identified, there is some evidence that females are associated with more intermediary trajectories such as "increasing", "late onset" or "early high" [37, 104]. These studies suggest there may be mechanisms that underpin membership into varying trajectories, but the extent to which this can be explained has yet to be fully understood. Females also appear to have a higher peak along these trajectories of depressive symptoms [93, 97, 99], and may reach this peak earlier than males [108], yet it is also not clear why this is the case.

6.3.1 The current study

Previous research has shown that trajectories of depressive symptoms tend to increase throughout adolescence and into young adulthood [37, 101], and that females are more likely to have higher trajectories of depressive symptoms [98, 99]. However, the longitudinal nature of depressive symptoms has yet to be fully understood as previous research has used small sample sizes, not had depressive symptoms data that spans a wide enough temporal window, and/or has been unable to measure depressive symptoms over important periods and transitions of development (e.g., from late childhood to adolescence and/or from adolescence into young adulthood). Likewise, no studies have identified critical periods of trajectories of depressive symptoms that could potentially highlight modifiable stages at which to best intervene. Identifying critical points such as the age of peak velocity of depressive symptoms (i.e., the age at which depressive symptoms are increasing most rapidly) could help researchers and clinicians target a stage of development where depressive symptoms might be increasing at the fastest rate, which may in turn prevent or reduce higher symptoms or the onset of depression.

The current study aims to address the previous limitations firstly by using multilevel growth-curve modelling to create trajectories of depressive symptoms in a large UK based population cohort. Multilevel growth-curve modelling has previously been a useful method for examining trajectories of depressive symptoms [102, 103]. Trajectories are created for both male and female populations between 10 and 22 years using 8 waves of depressive symptoms follow up. It was hypothesised that females would have higher trajectories of depressive symptoms throughout adolescence and young adulthood compared to males. Secondly, the ages of peak velocity and maximum depressive symptoms, as well as the depressive symptoms scores at both these ages for males and females are then calculated and compared. It was also hypothesised that the ages of peak velocity and maximum depressive symptoms would be earlier for females given their tendency to have elevated trajectories at the beginning of adolescence and that they commence on these trajectories earlier than

males.

6.4 Methods

6.4.1 Participants

As described in chapter 3, the data used in this chapter were taken from the Avon Longitudinal Study of parents and Children (ALSPAC).

6.4.2 Measures

Depressive symptoms: Depressive symptoms were measured on eight occasions between ages 10 and 23 using the short mood and feelings questionnaire (SMFQ) [129], as described in chapter 3. Further descriptive information for this chapter can be found in appendix 6.

Biological sex: Biological sex was identified from birth notifications around the time of delivery and coded as a dummy variable for being female (male = 0; female =1). See table 6.1 for sex specific SMFQ descriptive statistics.

Occasion	Male Sample Size	Female Sample Size	Mean Male SMFQ	Male SMFQ SD	Mean Female SMFQ	Female SMFQ SD
1	3,605	3,730	4.17	3.45	3.92	3.91
2	3,271	3,421	3.57	3.47	4.35	4.16
3	2,922	3,074	4.09	3.8	5.71	4.93
4	2,010	2,967	4.31	4.58	7.0	6.02
5	1,898	2,588	5.63	4.77	7.29	5.47
6	1,172	2,151	5.34	5.02	7.64	6.21
7	1,161	2,132	4.87	4.82	6.15	5.90
8	1,323	2,517	5.35	4.95	6.67	5.79

Table 6.1: Descriptive statistics for the Short Mood and Feelings Questionnaire (SMFQ) by sex

6.4.3 Statistical methods

Trajectories of depressive symptoms were estimated using multilevel growth-curve modelling [48, 49]. Descriptive statistics indicated the change in depressive symptoms followed a non-linear pattern (table 3.2). Thus the model needed to appropriately capture the non-linearity of these trajectories. A multilevel cubic growth-curve polynomial model was chosen for two reasons. First, entering age as a cubic polynomial fitted the data better and produced more plausible results than entering age as a quadratic or quartic polynomial (see appendix 6)[2]. Second, compared to more complex cubic splines and fractional polynomials which have also been used to model non-linear growth in other contexts [125, 135], entering age as a cubic polynomial led to a more parsimonious model. Multilevel cubic growth-curve polynomials have been used in previous studies examining trajectories of depressive symptoms [102, 103]. As in chapter 4, model fit was assessed using likelihood ratio tests and information criteria, consistent with other studies using multilevel growth-curve models [50, 102]. The preferred model specifies separate population-averaged trajectories for males and females by interacting the fixed-effects age polynomial terms with the female dummy variable. The age polynomial terms were allowed to vary randomly across individuals to capture each individual's unique trajectory. Very similar to the equations presented in chapter 4, the model can be written as:

$$\begin{aligned} y_{ij} &= \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 \\ &\quad + u_{0j} + u_{1j} t_{ij} + u_{2j} t_{ij}^2 + u_{3j} t_{ij}^3 \\ &\quad + e_{ij} \end{aligned} \tag{6.1}$$

where y_{ij} is the depressive symptom score and t_{ij} is the age for individual j at occasion i, x_{1j} is a dummy variable for being female, and u_{0j}, u_{1j}, u_{2j}, and u_{3j} are the random intercept, linear, quadratic and cubic effects of age, respectively. The occasion-specific residual e_{ij} allows the depressive symptom scores to deviate from the individual-specific cubic trajectories.

The random effects are assumed multivariate normal distributed with zero mean

[2]note: as stated earlier there were only eight occasions available at the time of this study and so a cubic polynomial model best fitted this data (even though later data resulted in a quartic model). This variation in model selection is unlikely to have any overall bearing on the results for this study (regarding critical points)

vector and constant covariance matrix:

$$\begin{pmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \end{pmatrix} \sim N \left\{ \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma^2_{u0} & & & \\ \sigma_{u01} & \sigma^2_{u1} & & \\ \sigma_{u02} & \sigma_{u12} & \sigma^2_{u2} & \\ \sigma_{u03} & \sigma_{u13} & \sigma_{u23} & \sigma^2_{u3} \end{pmatrix} \right\} \tag{6.2}$$

The elements of the covariance matrix summarise the degree to which individual-specific trajectories vary around the sex-specific population-averaged trajectories. The residuals are assumed normally distributed with zero mean and sex specific variance:

$$e_{ij} \; N\left(0, \sigma^2_{ej}\right) \tag{6.3}$$

which can be expanded to:

$$\sigma^2_{ej} = \alpha_0 \left(1 - x_{1j}\right) + \alpha_1 x_{1j} \tag{6.4}$$

All analyses were conducted using Stata 14 (StataCorp, College Station, TX, USA) using the user-written runmlwin command [134], which calls the standalone multilevel modelling package MLwiN v2.35 (www.cmm.bristol.ac.uk/MLwiN/index.shtml).

The population male and female trajectories are therefore given by:

$$Male : E\left(y_{ij} | t_{ij}, x_{1j} = 0\right) = \; \beta_0 + \beta_1 t_{ij} + \beta_2 t^2_{ij} + \beta_3 t^3_{ij} \tag{6.5}$$

$$\begin{aligned} Female : E\left(y_{ij} | t_{ij}, x_{1j} = 1\right) = \left(\beta_0 + \beta_4\right) + \left(\beta_1 + \beta_5\right) t_{ij} + \\ \left(\beta_2 + \beta_6\right) t^2_{ij} + \left(\beta_3 + \beta_7\right) t^3_{ij} \end{aligned} \tag{6.6}$$

Critical points: Several critical features were calculated from these sex-specific mean trajectories including: the ages of peak velocity of depressive symptoms (i.e., ages at which male and female depressive symptoms are increasing most rapidly), and the ages of maximum depressive symptoms (i.e., the ages at which male and

female depressive symptoms were the highest). The depressive symptoms scores were also calculated at each of these critical ages. The delta method in Stata was used to compare differences in the intercept, linear, quadratic and cubic terms, as well as at the critical points between the male and female trajectories. This was done to ease interpretation of the results. The delta method, which incorporates the estimate, standard errors and confidence intervals from post estimation results allows for wald test comparisons for non-linear models. This allowed me to explore differences of critical points with precision and uncertainty. See appendix 6 for further details.

6.5 Results

There were 9,301 individuals with data on sex and at least one measurement of the SMFQ, resulting in 39,942 measurements (17,362 male [43.47%]/22,580 female [56.53%]).

6.5.1 Trajectories of depressive symptoms

Females and males followed different trajectories (figure 6.1). The intraclass correlation evaluated at age 16 was 0.56 (SE = 0.01) indicating that over half of the variation in individuals' depressive symptoms at this age is captured by their individual-specific cubic trajectories. The correlation between the intercept (i.e., first measurement of depressive symptoms) and the slope (i.e., change in depressive symptoms with every year increase) was 0.52 (SE = 0.03). Table 6.2 presents the regression coefficients from the cubic polynomial model. The marginal sex-specific trajectories did not differ substantively with the addition of covariates (see Supplementary materials), so only the unadjusted trajectories and main features of the trajectories are described.

The differences in trajectories of depressive symptoms between males and females are shown in table 6.3 and figure 6.1. Briefly, females had higher trajectories compared to males, except between 10 and 11 years old where males were predicted to have higher depressive symptoms. Females were associated with higher depressive symptoms at 16 years of age (β = 6.7, SE = 0.07 [95% CI: 6.57, 6.83]) compared to males (β = 4.57, SE = 0.07 [95% CI: 4.43, 4.7]; $p^{DIFF} < 0.001$). Females had a higher linear slope (β = .049, SE = 0.02 [95% CI: 0.45, 0.53]) compared to males (β = 0.36, SE = 0.02 [95% CI: 0.31, 0.4]; $p^{DIFF} < 0.001$) which showed that depressive symptoms increased more rapidly for females until the age of 20. However, females had a greater negative quadratic slope (β = -0.04, SE = 0.002 [95% CI:

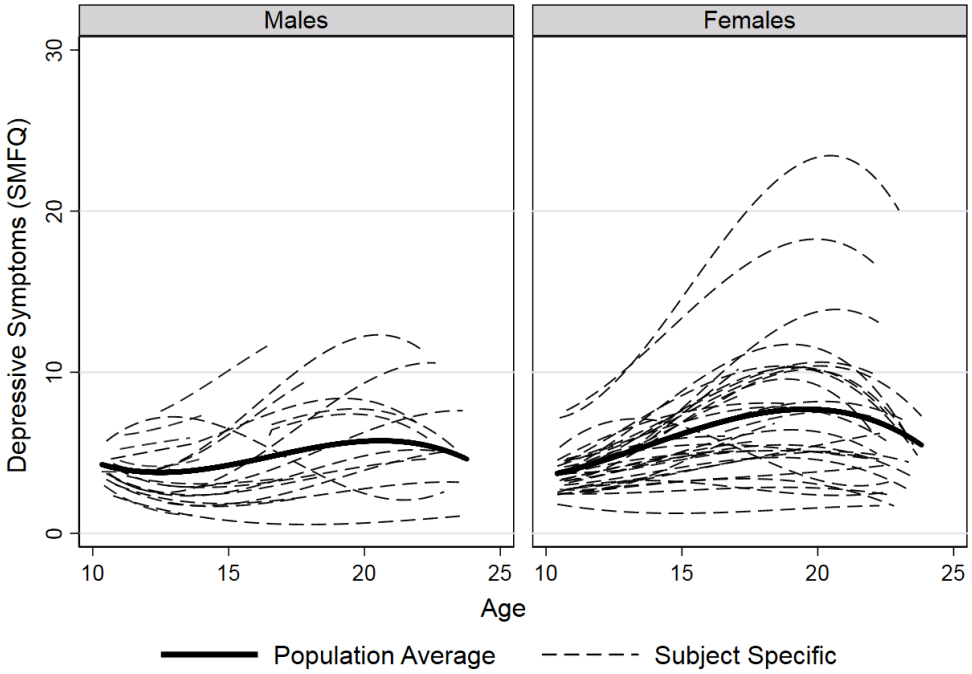
Parameter	Estimate	Std. Error	*p* value
Intercept	4.57 [4.43, 4.7]	0.07	<0.001
Age (slope)	0.37 [0.31, 0.4]	0.027	<0.001
Age^2 (acceleration)	0.01 [0.008, 0.02]	0.002	<0.001
Age^3 (cubic change)	-0.007 [-0.009, -0.006]	0.001	<0.001
Female	2.13 [1.95, 2.32]	0.1	<0.001
Female x Age	0.14 [0.06, 0.19]	0.03	<0.001
Female x Age^2	-0.05 [-0.06, -0.05]	0.003	<0.001
Female x Age^3	0.002 [0.0001, 0.003]	0.001	0.04
ICC	0.56		
Deviance	227890.58		

Table 6.2: Regression coefficients for the cubic polynomial model (n=9,301). 95% confidence intervals given in [parenthesis]

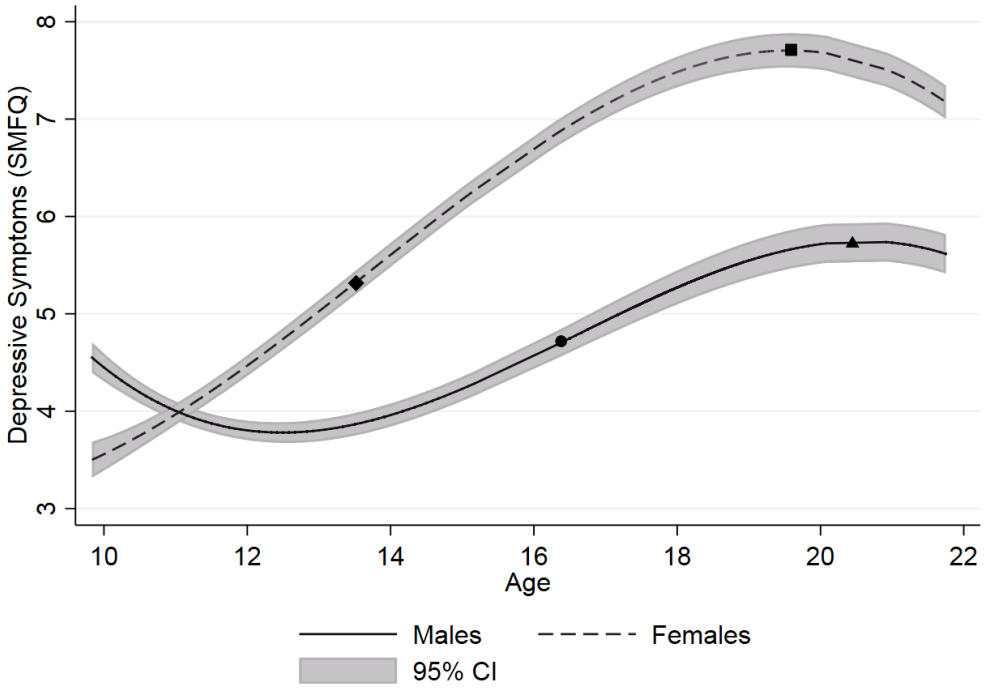
-0.05, -0.03]), suggesting from around age 20 their depressive symptoms started to decrease, in contrast to males (β = 0.01, SE = 0.002 [95% CI: 0.008, 0.2]; p^{DIFF} < 0.001). Finally, a negative cubic slope was observed for both females (β = -0.01, SE = 0.001 [95% CI: -0.001, -0.004]) and males (β = -0.007, SE = 0.001 [95% CI: -0.01, -0.006]; p^{DIFF} = 0.04), indicating that depressive symptoms were decreasing from age 20 onwards, however the current analysis suggested that both sexes decreased at similar rates into young adulthood (tables 6.2 and 6.3).

	Males	Females	Difference	*p* value
Intercept term for SMFQ	4.57 (0.07) [4.43, 4.7]	6.7 (0.07) [6.57, 6.83]	2.13 (0.1) [1.95, 2.32]	<0.001
Linear term for SMFQ	0.36 (0.02) [0.31, 0.4]	0.49 (0.02) [0.45, 0.53]	0.14 (0.03) [0.08, 0.19]	<0.001
Quadratic term for SMFQ	0.01 (0.002) [0.008, 0.2]	-0.04 (0.002) [-0.05, -0.03]	0.05 (0.003) [0.05, 0.06]	<0.001
Cubic term for SMFQ	-0.007 (0.001) [-0.01, -0.006]	-0.01 (.001) [-0.001, -0.004]	0.002 (0.001) [0.0001, 0.003]	0.04

Table 6.3: The intercept was centered to age 16 for interpretability. The differences between each term were calculated as follows: the intercept term for males (β_0) minus the intercept term for females ($\beta_0 + \beta_4$), the linear term for males (β_1) minus the linear term for females ($\beta_1 + \beta_5$), the quadratic term for males (β_2) minus the quadratic term for females ($\beta_2 + \beta_6$), the cubic term for males (β_3) minus the cubic term for females ($\beta_3 + \beta_7$). Standard errors are given in (parenthesis), 95% confidence intervals are given in [parenthesis]



(a) Individual and averaged population trajectories for a random set of 100 participants - by sex



(b) Averaged population trajectories for males and females. • Male age of peak velocity of depressive symptoms. ▲ Male age of maximum depressive symptoms. ♦ Female age of peak velocity of depressive symptoms. ■ Female age of maximum depressive symptoms

Figure 6.1: Cubic polynomial trajectories by sex. SMFQ: Short Mood and Feelings Questionnaire

6.5.2 Age of Peak Velocity and Age at Maximum Depressive Symptoms

The age of peak velocity in the model was earlier for females (13.51 years old, SE = 0.32 [95% CI: 12.88, 14.14]) compared to males (16.36 years old, SE = 0.1 [95% CI: 16.18, 16.55]; $p^{DIFF} < .001$). However there was little evidence of a difference between the age at the maximum point of depressive symptoms for females (19.61 years old, SE = 0.5 [95% CI: 18.63, 20.6]) compared to males (20.42 years old, SE = 0.14 [95% CI: 20.14, 20.69]; $p^{DIFF} = .13$). See table 6.4 for full statistics.

6.5.3 Depressive Symptoms Score at Age of Peak Velocity and at Age of Maximum Point of Depressive Symptoms

The predicted depressive symptoms scores at the estimated age of peak velocity were higher for females (5.42 points, SE = 0.06 [95% CI: 5.3, 5.55]) than they were for males (4.76 points, SE = 0.07 [95% CI: 4.62, 4.91]; $p^{DIFF} < .001$). The depressive symptoms scores at the maximum point of depressive symptoms were also higher for females (7.7 points, SE = 0.09 [95% CI: 7.52, 7.88]) compared to males (5.75 points, SE = 0.1 [95% CI: 5.55, 5.95]; $p^{DIFF} < .001$). See table 6.4 for full statistics.

	Males	**Females**	**Difference**	***p* value**
Age of Peak Velocity in SMFQ	16.36 (0.1) [16.18, 16.55]	13.51 (0.32) [12.88, 14.14]	2.86 (0.34) [2.2, 3.51]	<0.001
Age of Maximum SMFQ	20.42 (0.14) [20.14, 20.69]	19.61 (0.5) [18.63, 20.6]	0.80 (0.55) [-0.27, 1.88]	0.14
SMFQ at Peak Velocity	4.76 (0.07) [4.62, 4.91]	5.42 (0.06) [5.3, 5.55]	0.66 (0.1) [0.47, 0.85]	<0.001
SMFQ at Maximum Point	5.75 (0.1) [5.55, 5.95]	7.7 (0.09) [7.52, 7.88]	1.95 (0.14) [1.69, 2.22]	<0.001

Table 6.4: Calculated features from the trajectories of the cubic polynomial model. Standard errors are given in (parenthesis), 95% confidence intervals are given in [parenthesis]

6.5.4 Missing Data and Sensitivity Analysis

Missing data were handled using full information maximum likelihood (FIML), which assumes that data are missing at random. The initial analysis included individuals with at least one measurement from the SMFQ. Although individuals with

only one measurement do contribute to the analysis (e.g. via association between average depressive symptoms and sex), it is not meaningful to predict and examine trajectories for these individuals. To overcome this, a sensitivity analysis was run on a subset of individuals who had four or more depressive symptom scores. The sample size reduced from 9,301 to 5,409. However, removing these individuals had no substantive impact on the interpretation and conclusions from these trajectories (see appendix 6), thus only the full analysis is reported here. Results were also robust to the inclusion of covariates that are associated with missing data and attrition. Further analysis on individuals with depressive symptoms data at ages 10 and 22 revealed varying distributions of the depressive symptoms data and underlying demographics compared with individuals who only had depressive symptoms data at age 10 (i.e., had depressive symptoms data missing at 22), see appendix 6.

6.6 Discussion

The nature of trajectories of depressive symptoms between adolescence and young adulthood is not fully established, and research has yet to identify critical periods of trajectories of depressive symptoms that could potentially be used to target a stage of development where depressive symptoms might be increasing at the fastest rate. A greater understanding of the nature of depressive symptoms would aid researchers and clinicians in developing and improving treatments and interventions. The purpose of this analysis was to explore trajectories of depressive symptoms from childhood to young adulthood between males and females and to identify and compare critical points along these trajectories for both populations.

This analysis showed that females and males have different population-averaged trajectories of depressive symptoms, with varying ages of peak velocity of depressive symptoms. Using multilevel growth-curve modelling on 8 waves of data between ages 11 to 22, results suggest that females were on average associated with higher trajectories of depressive symptoms compared to males, with the exception of between 10 and 11 years old where on average males had higher depressive symptoms. Both male and female population-averaged trajectories increased during adolescence before declining in young adulthood, yet females on average had a higher rate of deceleration (depressive symptoms slowing down) from age 20 and both sexes had trajectories that first plateaued and then started to decline in young adulthood. Evidence suggested that that on average, females had an earlier age of peak velocity of depressive symptoms (i.e., age at which depressive symptoms is increasing most rapidly), but little evidence to indicate that females had an earlier age of maximum depressive symptoms (i.e., age at which depressive symptoms is highest on the tra-

jectory). Finally, depressive symptoms scores at the age of peak velocity and age of maximum depressive symptoms were both higher for females on average compared to males.

These findings support earlier hypothesis and previous research that trajectories of depressive symptoms increase from late childhood, through adolescence and begin to decrease in young adulthood [97, 99, 103]. One possible explanation for increased depressive symptoms during adolescence is that young people face a number of social, psychological and biological changes during this stage of development [16, 97]. These changes include transitioning between schools, making new friends, taking exams and experiencing puberty. As many studies highlight that trajectories of depressive symptoms increase during this period, efforts should be made to monitor individuals who show heightened depressive symptoms as they may be individuals at a greatest risk of depression or higher levels of depressive symptoms.

This chapter was also able to expand on previous work by estimating points on population-averaged trajectories marking the average age of peak velocity, of maximum depressive symptoms and the depressive symptoms scores at both of these ages. These results show the age of peak velocity of depressive symptoms was almost 3 years earlier for females. The results suggest that depressive symptoms are increasing most rapidly for females at approximately 13.7 years old and for males at 16.4 years old, and that treatment and interventions could be implemented at different ages for males and females. These findings have implications for clinical services, schools and parents, who should be made aware that females are more likely to be younger when depressive symptoms are increasing most rapidly, with males following at a later stage. Likewise, as females appear to have higher trajectories for a longer of period of time, more awareness could be targeted towards services, schools and parents over this period of heightened and increasing depressive symptoms. Identifying features such as the age of peak velocity may help determine at what age depressive symptoms are getting worse most rapidly, but also highlight a key characteristic of trajectories of depressive symptoms that is potentially modifiable. Future research should primarily examine if the age of peak velocity identified here is universal to other cultures and countries and should also look to examine other predictors of these ages to see if they are potentially modifiable. Given that individuals with higher starting points (intercepts), had steeper trajectories (slopes), it is important to identify depressive symptoms early and when they are increasing as the current results suggest that those who start with higher depressive symptoms are at a greater risk of continuing to have higher trajectories of depressive symptoms.

This chapters's findings suggested that the age of maximum depressive symptoms was approximately a year apart between males (20.7 years old) and females

(19.7 years old), although evidence for a difference was weak. Several studies have suggested that this age should occur around mid-to-late adolescence, approximately between 15-17 years old [99, 102, 103]. However, other evidence has indicated that this age of maximum depressive symptoms occurs later in development [93, 172], which coincides with the current results. There are several potential explanations as to why the current results observed a much later age of maximum depressive symptoms compared to some previous research. In several studies, the number of depressive symptoms measurements from follow-up are low and are therefore unable to pick up more nuanced changes in depressive symptoms over time. Depressive symptoms are dynamic and can change rapidly over a short period, thus researchers need frequent measurements to track subtle changes [51]. In the present analysis, the measurements were assessed on average never more than 3.5 years apart, which is more regular than many of the previous studies. It could be that frequently assessing depressive symptoms allowed detected changes and characteristics of the trajectories that were not observed in previous studies.

Another explanation is that variation in the age of maximum depressive symptoms is the result of contextual differences between the cohorts used. For example, similar ages of maximum depressive symptoms were observed using data from the National Longitudinal Study of Adolescents Health [37, 99], and the Canadian-based National Longitudinal Survey of Children and Youth [102, 103]. However, other research using different North American cohorts have observed later ages of maximum depressive symptoms [93, 172]. ALSPAC is one of the few longitudinal studies in the UK that currently has repeat depressive symptoms data across this period of development so it hard to conclude whether similar effects would be observed in other UK studies at this point. Other studies that examine depressive symptoms in longitudinal settings around the world use alternative methods to derive latent classes of trajectories of depressive symptoms [37, 43], and as such it is harder to compare critical points from these studies as there are often 4 or 5 trajectories from each study (each with their own age of maximum depressive symptoms). However, an important point to consider is that this analysis is the first to empirically estimate this age and present it with measures of uncertainty rather than simply describing it from figures. It is unlikely that this will explain the observed differences with other studies, but in the interest of interpretability and to help characterise the nature of trajectories of depressive symptoms, future research should estimate and report this age as this will help clarify whether there cross cultural differences for critical ages in the development of depression. Similarly, this is the first analysis to calculate and then compare critical points from two population trajectories (males vs. females). Interestingly, the current results supported previous research that suggested no sex differences between the ages of maximum depressive symptoms [93, 99], but con-

tradicted other research suggesting that females have an earlier age of maximum depressive symptoms compared to males [108]. However, the authors here did not use the same number of measurements, used a quadratic polynomial model and only had data that went up to approximately 18 years old. Future research should examine depressive symptoms regularly around these ages to see if the critical periods identified are similar across contexts. Such research will inform services, schools and parents about the nature of depression and how to prevent and treat it around these ages.

Still, it is not clear why females on average have higher trajectories of depressive symptoms and why females and males differ in their ages of peak velocity of depressive symptoms. One explanation is that women tend to experience puberty earlier than men and evidence has suggested that early pubertal timing may be a mechanism responsible for depression and higher depressive symptoms [16, 176]. Research has also shown that an earlier age of menarche is positively associated with higher depressive symptoms [132, 176] and a causal mechanism for greater depressive symptoms [177]. Transitioning through puberty is associated with other psychological and social changes, and individuals who transition early may not have developed the cognitive and emotional skills to combat these changes, and therefore experience lasting effects of depressive symptoms. Likewise, early pubertal changes could result in increased responsiveness to stressors in females, resulting in higher depressive symptoms [16]. These findings suggest that individuals with higher starting points, had higher trajectories. Therefore an earlier age of higher depressive symptoms may set an individual up for a higher trajectory which takes longer to recover from. This could explain why females have higher trajectories compared to males, although more research using the timing and changes in pubertal status for both males and females would be needed to substantiate this claim.

Additionally, Angold and colleagues found that depression was higher for females between the ages of 9 and 16, and this seemed to coincide with both pubertal status and timing of puberty [178]. Of note, the number of girls with depression in their study was highest at around age 14, which coincides with the age of peak velocity of depressive symptoms in the present analysis. This suggests there may be some common mechanism at this age that is underpinning depressive symptoms, and how this manifests. The age of peak velocity from the current analysis tends to match the ages at which both males and females experience puberty and so one possible reason why the current analysis observed varying ages of peak velocity of depressive symptoms between males and females may be through the role of puberty.

Despite a number of strengths, this analysis has several limitations that should be highlighted. One limitation that arises with the data used here, and more gen-

erally with longitudinal data, is attrition and the role this plays in biasing results towards individuals who respond. The sample size in this analysis decreased from 7,335 at the first wave of data collection to 3,840 by the eighth occasion opening the possibility to potential attrition bias. Analysis on individuals with depressive symptoms data at both the first and last occasion, compared to those with depressive symptoms data at the first occasion but not the last, revealed differences in the overall symptoms scores and underlying demographics. However, this is consistent with previous research [108], and suggests that studies with attrition could be underestimating the effect of sex differences in trajectories of depressive symptoms as females were more likely to have not responded at the last occasion. Previous studies have also imputed missing data utilising a missing at random approach (MAR) but found that bias due to systematic missingness in ALSPAC is not substantial [26, 179]. The multilevel growth-curves models used in the present analysis also use FIML to account for missing data and sensitivity analyses revealed that the main effects of this analysis (i.e., the trajectories and the critical points) were not substantively affected by the inclusion of covariates associated with missing data and attrition bias. Nevertheless, future studies should highlight missing data patterns and attempt to account for data that could potentially be missing not at random. A more thorough discussion regarding missing data and potential biases is given in the conclusions chapter.

Another limitation in this analysis stems from the choice of model used and the assumptions made with multilevel growth-curve models. Modelling trajectories of depressive symptoms appropriately is challenging. A cubic polynomial model was chosen given it is a more parsimonious approach in comparison to splines and fractional polynomials and that it has been used in previous studies that show nonlinearity [101, 102]. However, alternative approaches such as a restricted cubic spline model may fit the data better at the expense of parsimony. Similarly, a quartic polynomial model may be a better model if the depressive symptoms data continues to rise. Cubic terms (and other polynomials) may also perform poorly at the start and end of the trajectories, as well as potentially producing artificial turns in the data that do not exist [61]. Checks were made to ensure that no artificial turns occurred in the data by comparing against other models and the underlying data and descriptive statistics for plausibility. Additionally, the age of peak velocity of depressive symptoms and age of maximum depressive symptoms were calculated well within the range of the trajectories so any bias from potentially mismodelling the start and end of the trajectories is minimised.

A similar limitation in this analysis is in regard to highlighting variability with the multilevel growth-curve model. A problem with population growth curves like

the ones used in the present analysis is that it is harder to convey how much variability exists across the population, compared to other methods such as latent class growth analysis or growth mixture modelling, which typically stratify population trajectories into multiple subpopulation trajectories. Future research could derive critical periods from latent class analysis to examine if certain groups of trajectories have earlier ages of peak velocity or later times of maximum depressive symptoms. Such research could further highlight variability in critical points across multiple trajectories.

6.7 Conclusion

The nature of trajectories of depressive symptoms between adolescence and young adulthood is not yet clear, but research has suggested that increased levels of depressive symptoms throughout this period are associated with a greater risk of psychopathology and adverse social outcomes in later life [20, 43]. It is important to examine the nature of depressive symptoms and identify critical periods that could potentially be used to target a stage of development where depressive symptoms are increasing at the fastest rate. A greater understanding of these two facets would aid in developing and improving treatments and interventions. This chapter examined trajectories of depressive symptoms between males and females in a large UK based population cohort over multiple stages of development. Using multilevel growth-curve models, the findings suggested that females on average were associated with steeper trajectories of depressive symptoms compared to males, indicating they were more likely to experience higher depressive symptoms for longer. Importantly, the age at which depressive symptoms were increasing most rapidly were much earlier for females on average compared to males. Whilst the mechanisms underpinning this sex difference are not entirely understood, pubertal status and the timing of pubertal status could play a role in explaining why females on average have higher trajectories and commence on these trajectories earlier than males. Calculating the age of peak velocity of depressive symptoms is a potentially useful tool for exploring how depressive symptoms are changing and at what age they are increasing most rapidly, which may have consequences downstream. If this can be used for clinical purposes, it may be possible to treat individuals at this age, which may help reduce depressive symptoms or depression at a later stage.

6.8 Chapter summary

This chapter has shown that female sex is a strong risk factor for higher population-averaged trajectories of depressive symptoms and supports the work highlighted in the previous chapter (that female sex is associated with the four "higher" trajectories), and research identified in the literature review. This chapter has addressed the second research objective by showing the association between sex and trajectories of depressive symptoms, the third research objective by identifying critical points in trajectories and the fourth research objective by simplifying some of the estimates taken from the cubic polynomial growth curve model. This chapter has also shown that the estimation of critical points in trajectories (such as the age of peak velocity) could be used for preventing depressive symptoms from increasing or highlighting a potentially important period when depressive symptoms could be targeted. These results expand upon the findings of chapters 4 and 5, and previous research through this notion of identifying critical points, but is limited by only focusing on one risk factor (sex). In the next chapter, I build upon this work and the findings from chapter 5 by using a different risk factor (childhood trauma) and then translating the results in a simpler manner than what is presented here and in previous research.

Chapter 7

Childhood Trauma and Trajectories of Depressive Symptoms Across Adolescence

7.1 Chapter outline

This chapter expands upon the findings from chapters 4, 5 and 6 by using the population-averaged trajectories approach to probe the association between childhood trauma and later trajectories of depressive symptoms. Chapter 4 identified the trajectories across adolescence and young adulthood. Chapter 5 then used a multivariate approach to exploring risk factors for trajectories of depressive symptoms, and found that exposure to childhood bullying was strongly associated with higher trajectories - indicating that environmental risk factors such as bullying could be important for heightened depressive symptoms across adolescence and young adulthood. Likewise, chapter 6 demonstrated how a risk factor could be explored in greater detail using the population-averaged approach. In this chapter, I explore how childhood trauma (which can be thought of as an extension of bullying) and the number of childhood traumas (which can be thought of as an accumulation of negative environmental events) are association with later trajectories of depressive symptoms in an attempt to expand upon the previous chapters. Here I use the population-averaged approach and extend the findings from the previous chapter to show how estimates from complex trajectory models can be translated into simpler findings through an "alternative model parametrisation". I show how this alternative framework could be useful for determining when a risk factor is likely to have its greatest effect on depressive symptoms (and how this may differ for different populations) and how it extends the traditional growth curve approach, which could be

useful for clinicians policy makers downstream.

This chapter mainly addresses the second research objective: "how are genetic and environmental risk factors differentially associated with varying trajectories of depressive symptoms?", and the fourth research objective: "can the results from trajectory models be simplified to aid in the interpretation and translation of findings?" but it also touches upon third research objective: "are there critical points of trajectories of depressive symptoms which tell us more about how and when depression changes across adolescence?" This chapter is the culmination of chapters 4, 5 and 6 and was written with a narrative that aimed to help the reader better interpret complex trajectory estimates - thus the structure of this chapter varies from chapters 5, 6 and 8. Part of this chapter was adapted to be manuscript which is currently under review at Social Science and Medicine: Population Health. All supplementary materials for this chapter are provided in appendix 7.

Kwong, A. S. F., Maddalena, J. M., Croft, J., Heron, J., Leckie, G. (Under Review at Social Science and Medicine: Population Health). Early Childhood Trauma and Trajectories of Depressive Symptoms.

7.2 Chapter abstract

Growth curve modelling such as trajectory analysis is useful for examining the longitudinal nature of depressive symptoms, their antecedents and later consequences. However, issues in interpretation associated with this methodology could hinder the translation from results to policy changes and interventions. The aim of this article is to provide a "model interpretation framework" for highlighting growth curve results in a more interpretable manner. Here I demonstrate the association between childhood trauma and trajectories of depressive symptoms. Childhood trauma has been shown to a be strong predictor for later depression, but less is known how childhood trauma has an effect throughout adolescence and young adulthood. Identifying when childhood trauma (and its severity) is likely to have its greatest impact on depression is important for determining the timing of interventions for depression.

I used data on over 6,500 individuals from the Avon Longitudinal study of Parents and Children (ALSPAC) to estimate trajectories of depressive symptoms between the ages of 11 and 24. Depressive symptoms were measured using the short mood and feelings questionnaire (SMFQ) across 9 occasions. Childhood trauma was assessed between the ages of 5 and 10 years old, and I estimated population averaged multilevel growth curves of depressive symptoms for exposure to trauma (yes vs no) and then in a separate model, the number of trauma types reported such as inter-

personal violence, abuse or neglect (coded as 0, 1, 2, 3+). I then calculated what the depressive symptoms scores would be ages 12, 14, 16, 18, 20, 22, 24, between these varying trajectories.

Reported exposure to childhood trauma was associated with less favourable trajectories of depressive symptoms across adolescence, mainly characterised by exposed individuals having worse depressive symptoms at age 16. There was an exposure-response relationship between the number of childhood traumas and trajectories of depressive symptoms. Individuals exposed to 3 or more types of trauma had substantially steeper and less favourable trajectories of depressive symptoms: becoming worse at a more rapid rate until the age of 18. By age 18, individuals that reported the greatest exposure to trauma (3+ types of trauma) had 14% greater depressive symptoms compared to non-exposed participants.

Childhood trauma is strongly associated with less favourable trajectories of depressive symptoms across adolescence. Individuals exposed to multiple types of inter-personal violence, abuse or neglect are at the greatest risk of worsening depressive symptoms throughout adolescence and young adulthood. Individuals exposed to traumatic experiences in childhood should be identified as at high risk of depression and other adverse outcomes as early trauma may disrupt social development and have lasting consequences on mental health outcomes. The model interpretation framework presented here may be more interpretable for researchers, clinicians and policy makers as it allows comparisons of depression across multiple stages of development to highlight when the effects of depression are greatest.

7.3 Introduction

Growth curve modelling is useful for examining the longitudinal nature of depression across development [32, 172]. Growth curve models allow researchers to estimate trajectories that describe patterns of change in depressive mood over time. These are potentially more useful than analysis of data from any single occasion, as it is possible to estimate the longitudinal nature of depression across periods of development and transitions. Furthermore, it is possible to examine the antecedents of varying trajectories of depressive symptoms [80, 98], their later consequences [43, 67], their relationship with other co-occurring traits [5, 76, 180] and the identification of critical points that could be translated into preventions and interventions (as shown in the previous chapter). Consequently, growth curve or trajectory analysis is not only a useful tool for research, but also potentially for clinical inference and identifying at risk groups for treatment [30].

Methodology exploring trajectories of depressive symptoms has been increasingly used in recent years [30–32]. However, much of this research has yet to impact on policy and clinical inference, which could be a result of difficulties in translating findings to inference. Estimating trajectories of depressive symptoms can be done in several ways: one approach is to plot the mean scores by age and depressive symptoms and compare differences at each age (i.e., with a t-test/ANOVA). However, one problem with this approach is that there may be different samples at the various ages, and this can lead to biased estimates with missing data. A more popular approach is to stratify population trajectories into multiple sub-group trajectories (e.g., latent classes growth analysis or growth mixture models, see [41]). An alternative approach is to estimate population-averaged trajectories, with individuals being allowed to vary around this population average (e.g., multilevel growth-curves and structural equation models, see [59]). These latter approaches quantify the degree of change, making them useful methods for estimating how depression changes over a certain period of time, and what might predict this change. These two approaches are somewhat similar but can produce different results and interpretations, thus harmonising results from both analyses is challenging and could impact on how clinicians and policy makers interpret and implement these findings.

As highlighted in the literature review and throughout this these, one issue with the longitudinal analyses of depressive mood is that depressive symptoms fluctuate and are characterised by periods of rapid growth, severity and varying ages of onset [103], especially during heightened risk periods such as adolescence [16]. In many studies, modelling trajectories of depressive symptoms and the subsequent interpretation is complex and not easily understood. For example, changes in depression are rarely linear. Studies may typically use higher order polynomials to model non-linear trajectories (e.g., quadratic and cubic functions of age), which can result in complicated model estimates (positive quadratic terms but negative cubic terms etc). This can be seen in chapter 6 for example). In turn, this can be difficult for researchers and clinicians to interpret and inform policy and practise. To combat this, researchers often use illustrations of trajectories to highlight complex results, however in many cases [97, 102, 103], these illustrations: 1) do not come with degrees of certainty (i.e., confident intervals) 2) can be difficult to compare when there are multiple trajectories that cross and overlap (even with certainty levels) and 3) do not precisely define key characteristics of the trajectory such as estimating when the trajectory is at it's highest or lowest (the terminology used will often be vague using words like "approximately" or "around"). Therefore, whilst graphical representations of trajectories are useful to an extent, it is important to find alternative ways to highlight and further supplement results from trajectory methods. An example of this has been demonstrated in longitudinal assessments of autistic traits

[181]. Here, Mandy and colleagues estimated differences in the predicted autistic traits scores between male and female trajectories at multiple ages and were able to quantify the exact age where autistic traits began to change.

This approach could be beneficial when applied to the longitudinal study of depressive symptoms. It is often important to not only highlight the course of depression over time, but also when differences may be occurring and how two or more trajectories (i.e., exposed vs not exposed) differ at a certain stages of development (i.e., is one higher at a particular time). The results in many studies highlighting differences between trajectories are not straight forward, as the presented estimates are typically the estimated coefficients of polynomials and the coefficient of each term in the polynomial is hard to interpret in isolation. More clarity in this area could assist clinicians and policy makers to understand the implications of results from analyses of trajectories of health outcomes, but could also shed light on interesting results from the models (such as empirically testing when a trajectory is "higher" than another and how this changes across time). Therefore, the first aim of this analysis is to highlight how the results from these analyses can be made more interpretable to researchers, clinicians and policy makers by presenting an alternative model interpretation framework to highlight results that show the depressive symptoms scores of different trajectories at different ages. This framework essentially calculates what the depressive symptoms scores would be for an exposed trajectory at a given age (i.e., 12, 14 or 16...) and compares it to the age of an unexposed group at the same age. This gives a depressive symptoms score that can be quantified and compared at numerous stages of development to help translate complex estimates and help determine when depressive symptoms may be changing or at their greatest/lowest.

One of the most useful applications for growth curve modelling is to examine how early antecedents or risk factors may predict the trajectory of depressive symptoms over time. In chapter 5, I showed that childhood bullying was strongly associated with the "higher" trajectories of depressive symptoms, providing further evidence that traumatic events in childhood can have persistent effects on depressive symptoms. Bullying is one traumatic event that children may be exposed to, however less is known about more general forms of childhood trauma. Therefore, this chapter looked to expand upon previous chapters by examining the association between childhood trauma and trajectories of depressive symptoms across adolescence and young adulthood. Childhood traumas is a key predictor for adolescent and young adulthood depression [182–184], yet its effect on depressive mood throughout the course of adolescence and young adulthood is still not clear.

Latent class analysis has found that exposure to abuse before the age of 18 years old is associated with less favourable trajectories of depressive symptoms [104].

Here, Olino and colleagues found that individuals who scored higher on a scale of childhood adversity and abuse has increased odds of belonging to the 'persistent', 'increasing' and 'initially high' trajectories, but interestingly not the 'later onset' trajectory of depressive symptoms. Maltreatment in childhood has also been associated with steeper trajectories of depressive symptoms, and those who experienced sexual abuse younger were more likely to have trajectories that started off higher, but then reduced over time [185, 186]. These results suggest that the effects of childhood trauma may have more damaging effects during the formative years of adolescence, as opposed to an increased risk of depression at a later age. There is also evidence to suggest that more stressful negative events in childhood are associated with higher trajectories of depressive symptoms in other longitudinal studies [34, 36, 74, 106]. However, in many of these studies, depressive symptoms are not measured across the entire period of adolescence and therefore the true longitudinal nature of childhood trauma on trajectories of depressive symptoms is not known.

For population averaged trajectories, the relationship between childhood trauma and trajectories of depressive symptoms is less clear. Recent studies have suggested that adverse childhood experiences including abuse and neglect were associated with less favourable trajectories of depressive symptoms [187] and that increased stressful negative events were associated with a steeper slope for trajectories of depressive symptoms across adolescence, that began to decrease in young adulthood [18, 97]. Identifying when childhood trauma is likely to have its greatest impact on depression throughout adolescence and young adulthood is important for indicating when interventions and support may be most beneficial. Currently, there is a paucity of knowledge on when childhood trauma is likely to have the greatest impact on trajectories of depressive symptoms. There is also some evidence to suggest that childhood trauma and stressful life events are not associated with worsening trajectories [80, 86]. However, I note that in one of these studies, negative life events were assessed by parental report [80], which could lead to an underreporting of the exposure.

Research has also yet to focus on how the number of types of traumatic experiences may predict the longitudinal nature of depression. Multiple traumas (or polyvictimisation) represent an accumulation of different types of traumas (i.e., abuse, neglect and violence) and evidence suggests traumatic expereicnes are often not isolated incidents (they often co-occur) [188]. Therefore, it is important to consider multiple traumatic experiences and not just bullying for example. There is some evidence to suggest that the number of negative events in childhood may partially explain the extent to which the risk of depression is increased by exposure to trauma, as more than two negative life events early in childhood have been asso-

ciated with higher trajectories of depressive symptoms [34]. However, little is known about the number of types of traumatic experiences in childhood and later trajectories of depressive symptoms. Life-course models suggest that an accumulation of negative events may be more harmful than traumatic exposure on a single occasion [124]. It is therefore important to examine if the number of types of childhood traumatic experiences might differentially predict varying trajectories of depressive symptoms across adolescence.

Thus, the second aim of the current analysis is to build upon previous research by examining the association between childhood trauma and trajectories of depressive symptoms across adolescence and young adulthood. I was also interested in extending previous research by investigating how this association might change depending on the number of types of childhood traumatic experiences.

7.4 Methods

7.4.1 Sample

As described in chapter 3, the data were taken from the Avon Longitudinal Study of Parents and Children (ALSPAC).

7.4.2 Measures

Depressive symptoms

Self-reported depressive symptoms were measured on nine occasions between ages 10 and 24 using the short mood and feelings questionnaire (SMFQ) [129]. Further information can be found in chapter 3.

Childhood trauma

Two measures of trauma were used for this analysis derived from previous analysis [189, 190]: (1) A binary measure of inter-personal violence, abuse and neglect during mid-childhood (age 5-10.9 years; [no=0; yes=1]) and (2) the number of trauma types reported during mid-childhood (0, 1, 2 or 3 or more [3+]). Briefly, these variables were derived from 121 self-report and parent report questions about traumatic experiences and cover six domains of trauma: physical abuse, emotional abuse, bullying, sexual abuse, domestic violence and emotional neglect. The data used to create these variables were taken from multiple trauma questions collected from both parents and children regarding exposure to these traumas.

Confounders

The following confounders were included based upon previous literature examining early social risk factors and trajectories of depressive symptoms [75, 115]: sex (coded as a dummy variable for being female [male = 0; female =1]), maternal postnatal depression (no vs yes), maternal occupational status at birth (manual vs non-manual), maternal educational attainment at birth (A-level or higher vs O-level vs < O-level) and parity (1st born vs 2nd born vs 3rd born or more).

Statistical methods

As stated in in chapter 4, trajectories of depressive symptoms were estimated using multilevel growth-curve modelling [59, 131]. Briefly, I was able to use nine occasions for this analysis and so I chose to use a multilevel quartic age polynomial growth-curve model (i.e., the preferred model fit from chapter 4). Age was first grand-mean centred around 16.53 years (the mean age of all assessments) in order to improve interpretation [101, 102], since model intercept and intercept variance then correspond to the middle of adolescence.

I ran separate models to examine the association between each trauma variable and these trajectories of depressive symptoms. The first model examined population-averaged trajectories for the exposure to trauma (no vs yes) by interacting the fixed-effects quartic age polynomial terms with the "any trauma" dummy variable. This produced two trajectories of depressive symptoms corresponding to the sub-populations with and without trauma. The second model repeated this approach by entering dummy variables representing the number of traumatic experiences (1, 2 and 3+). In all the analyses, the quartic polynomial age terms varied randomly across individuals to capture each individual's unique trajectory. Model equations are given in appendix 7.

I then predicted depressive symptoms scores at each of the following ages: 12, 14, 16 18, 20, 22 and 24, separately for each population averaged trajectory. I used the delta method to compare these predicted scores across the different trajectories at each of these ages. All analyses were conducted using Stata 15, yet for the analysis using the delta method, non-linear comparisons were estimated using the 'nlcom' command in Stata. The delta method used here relies on nonlinear transformations of the estimated parameters from a model to calculate the variance, standard error and Wald test statistic. This essentially means that when comparing depressive symptoms scores at various ages, we can use the beta, standard error and confidence intervals to calculate and compare differences. Model equations and additional information are provided in appendix 7.

Missing data

Missing data in the repeated measures data were again handled using full information maximum likelihood (FIML), which assumes that data are missing at random [138].

7.5 Results

7.5.1 Sample characteristics

Participant demographics are described in table 7.1. Additional descriptive statistics and reliability measures for the SMFQ are described in chapter 3 and appendix 7. There were 6,711 individuals with data on the number of traumas, at least one measurement of depressive symptoms and all confounders. The interpretation of the results did not vary substantially with the inclusion of confounders, thus only the adjusted analysis are reported here. Unadjusted analyses are reported in appendix 7.

	No Trauma	1 Trauma	2 Traumas	3+ Traumas	x^2, p
Sex					
Males n (%)	2,607 (45.70)	1,166 (54.13)	355 (49.44)	141 (47.64)	45.04, p <.001
Females n (%)	3,907 (54.30)	988 (45.87)	363 (50.56)	155 (52.36)	
Maternal Education					
A Level or Higher n (%)	2,197 (40.60)	838 (40.60)	293 (42.80)	125 (43.20)	3.17, p = 0.79
O Level n (%)	1,904 (35.20)	737 (35.70)	242 (35.40)	97 (33.60)	
<O Level n (%)	1,311 (24.2)	489 (23.70)	149 (21.80)	67 (23.20)	
Maternal Occupational Status					
Non-manual n (%)	1,890 (40.80)	704 (40.30)	251 (42.80)	95 (40.20)	1.14, p = 0.77
Manual or lower n (%)	2,743 (59.20)	1,043 (59.70)	336 (57.20)	141 (59.80)	
Parity					
First Born n (%)	2,485 (45.20)	996 (48.20)	320 (46.90)	117 (41.30)	9.09, p = .169
Second Born n (%)	1,998 (36.40)	704 (34.10)	233 (34.10)	106 (37.50)	
Third Born + n (%)	1,012 (18.40)	367 (17.70)	130 (19.00)	60 (21.20)	
Maternal Postnatal Depression					
No n (%)	4,849 (92.60)	1,790 (89.10)	587 (87.30)	288 (81.10)	68.67, p <.001
Yes n (%)	388 (7.40)	219 (10.90)	85 (12.70)	53 (18.90)	

Table 7.1: Participant demographics for the number of traumas. Parenthesis represent column percentages

7.5.2 Direct model output vs alternative model parameterisation

Estimates from each trauma model can be parameterised in two ways. As the trauma variables were coded as dummy variables for both any trauma variable (coded as 0/1) and number of traumas (coded as 0/1/2/3+), the 0 coded dummy variable can be thought of as the baseline trajectory. Therefore, the effect of trauma (being coded as 1) or the number of traumas (coded as 1/2/3+) are 'added' onto the baseline trajectory to represent the effect of having any trauma/number of traumas. As shown in tables 7.2 and 7.3, the direct model output shows the intercept and age term coefficients in the dummy variable regression format. However, it is also possible to calculate an alternative parameterisation of the model in a more interpretable manner by showing the complete trajectory estimates for an individual with no trauma compared to an individual with trauma or the number of traumas. This is achieved by adding the coefficient of the trauma variable onto the coefficient of the reference variable which then calculates the intercept or age terms for each distinct population trajectory.

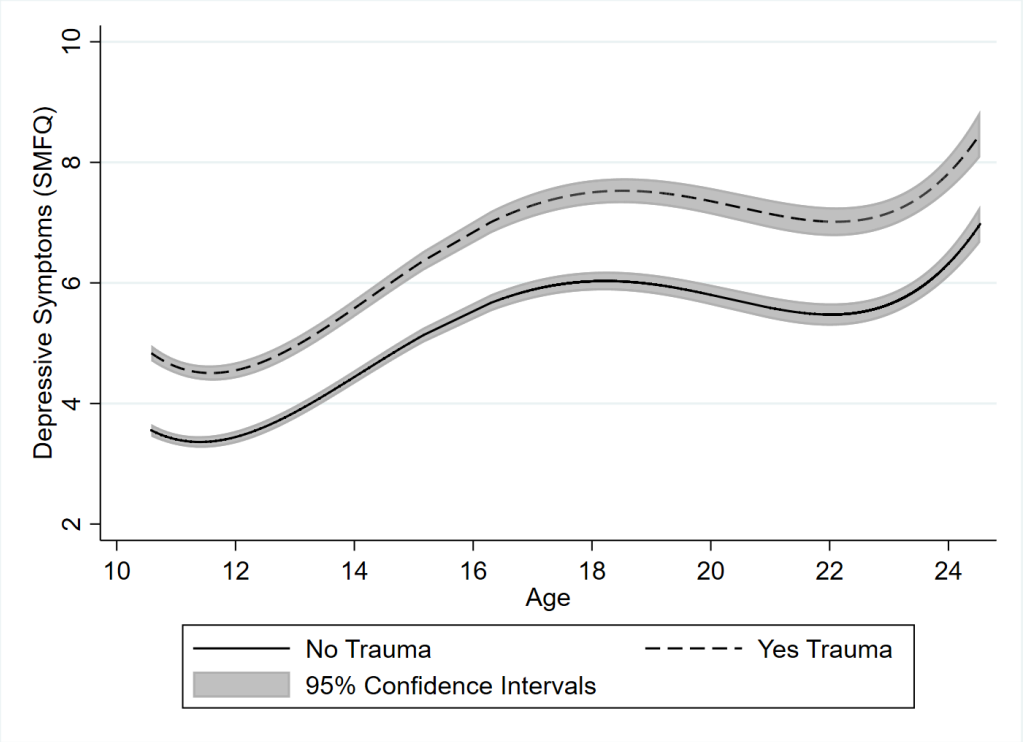
7.5.3 Association between any trauma and trajectories of depressive symptoms

As shown in figure 7.2.a, individuals exposed to trauma (between ages 5-10) had worse trajectories of depressive symptoms compared to those who had not experienced trauma. Both trajectories increased throughout adolescence until the age of 18, where symptoms decreased. However, symptoms then began to rise again from the age of 22. The main differences between the two trajectories were characterised by individuals exposed to trauma having a higher intercept[1] at age 16 (β = 6.4, SE= 0.13 [95% CI: 6.15, 6.65]) compared to non-trauma exposed individuals ((β = 5.17, SE= 0.11 [95% CI: 4.96, 5.38]; $p^{DIFF} < .001$). There was a weak association between individuals exposed to trauma and the linear age term (β = 0.38, SE= 0.03 [95% CI: 0.33, 0.43]), compared to non-trauma exposed individuals (β = 0.32, SE= 0.02 [95% CI: 0.28, 0.36]; $p^{DIFF} = .09$), which showed that individuals with trauma may have higher linear growth. However, there was no association between the remaining age terms (e.g., quadratic, cubic and quartic age terms) and the non-trauma and trauma exposed individuals ($ps^{DIFF} = .11$), suggesting that overall growth was not substantially different between the two trajectories. Full estimates are shown in table 7.2.

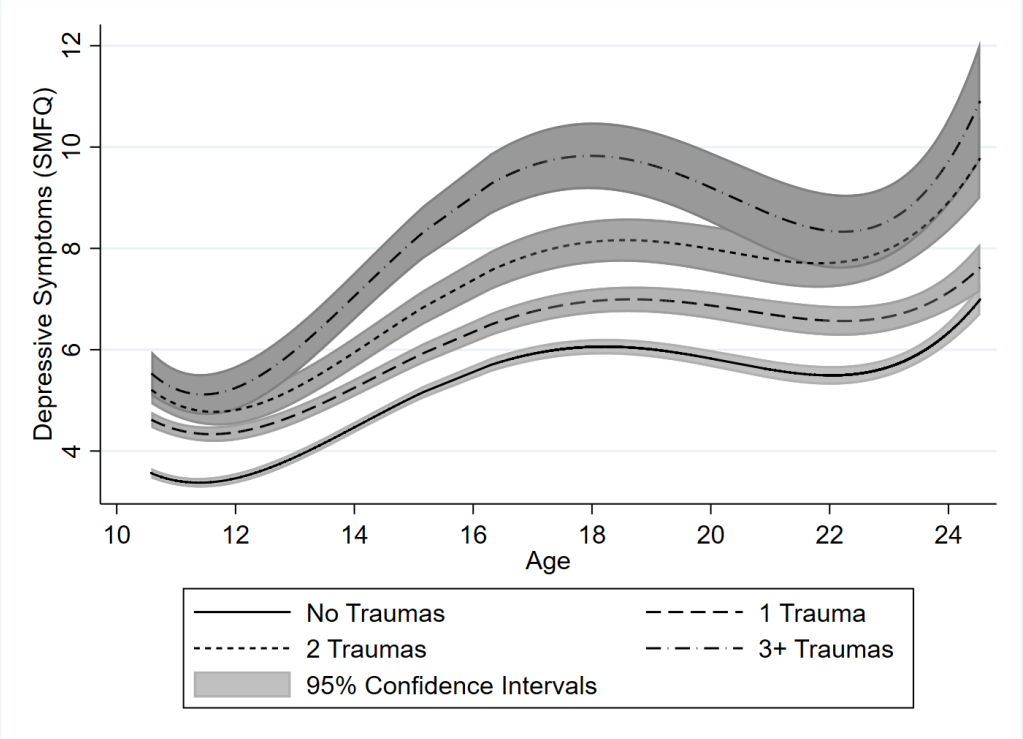
[1]Intercepts were centered to 16.53 years, the grand mean age. Centering the intercepts is common practice and allows for easier interpretation

	Direct Model Output			Alternative Parametrisation		
Parameter	**Estimate**	**Std. Error**	***p* value**	**Estimate**	**Std. Error**	***p* value**
No Trauma Intercept	5.17 [4.96, 5.38]	0.11	<.001	5.17 [4.96, 5.38]	0.11	<.001
No Trauma x Age	0.32 [0.28, 0.36]	0.02	<.001	0.32 [0.28, 0.36]	0.02	<.001
No Trauma x Age^2	-0.10 [-0.11, -0.08]	0.01	<.001	-0.10 [-0.11, -0.08]	0.01	<.001
No Trauma x Age^3	-0.004 [0.01, -0.003]	0.001	<.001	-0.004 [0.01, -0.003]	0.001	<.001
No Trauma x Age^4	0.002 [0.001, 0.002]	0.0001	<.001	0.002 [0.001, 0.002]	0.0001	<.001
Yes Trauma Intercept	1.23 [0.97, 1.49]	0.13	<.001	6.40 [6.15, 6.65]	0.13	<.001
Yes Trauma x Age	0.06 [-0.01, 0.12]	0.03	0.09	0.38 [0.33, 0.43]	0.03	0.09
Yes Trauma x Age^2	-0.001 [-0.02, 0.02]	0.01	0.95	-0.10 [-0.11, 0.08]	0.01	0.95
Yes Trauma x Age^3	-0.001 [-0.003, 0.003]	0.001	0.11	-0.006 [-0.007, 0.005]	0.001	0.11
Yes Trauma x Age^4	0.0001 [-0.0003, 0.0005]	0.0002	0.69	0.002 [0.001, 0.002]	0.0002	0.69
Deviance			189554.21			

Table 7.2: Childhood trauma estimates. The no trauma variable should be viewed as the reference category as trauma was coded as a dummy variable (0/1). Thus, the intercept coefficient (and the coefficients for subsequent age terms) for an individual with trauma are the trauma intercept + yes trauma intercept (i.e., $\beta_0 + \beta_5$). The same applies for all age terms. The Alternative Parametrisation results can therefore be thought of as the calculated scores and therefore the β_x refer to the direct model output only. The standard error and p-value correspond to the differences between the trauma estimates and the no trauma differences. The adjusted analysis included confounders (all entered as main effects) child sex, maternal postnatal depression, maternal education and social economic status at birth and parity. Intercepts are centred to age 16, the mean age of all assessments



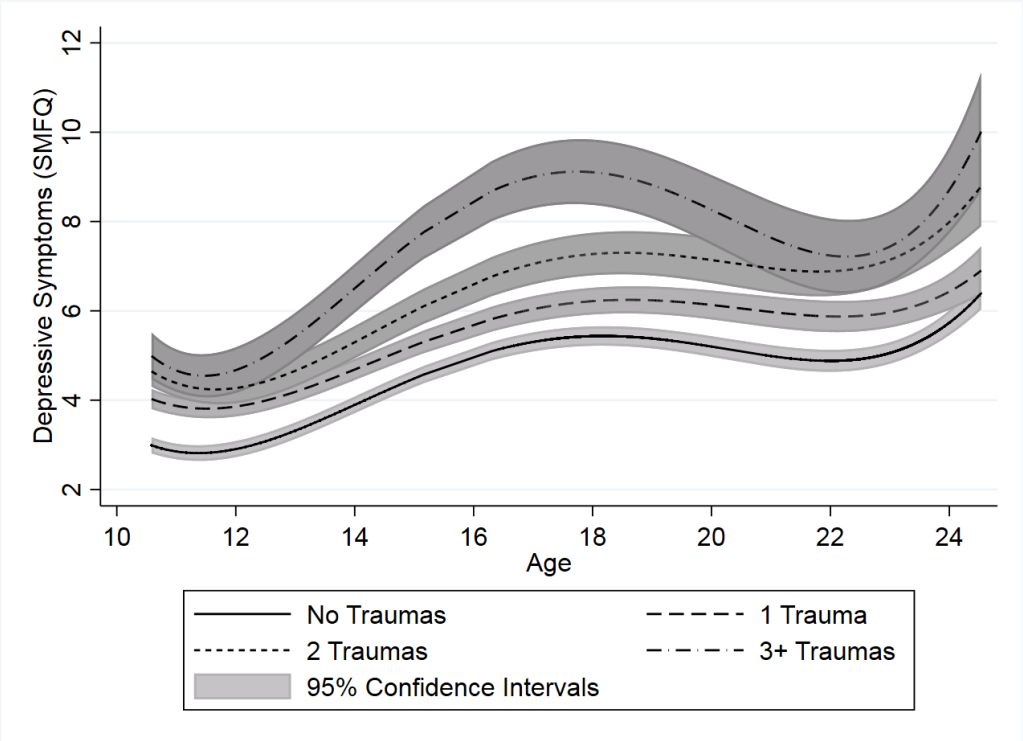
(a) Unadjusted adjusted association between any trauma (between 5-10 Years) and SMFQ trajectories. Differences between the trajectories are given in the adjusted results (figure 7.2)



(b) Unadjusted association between number of trauma types (between 5-10 Years) and SMFQ Trajectories

Figure 7.1: Unadjusted association between childhood traumas and trajectories of depressive symptoms. SMFQ: Short Mood and Feelings Questionnaire

(a) Adjusted association between any trauma (between 5-10 Years) and SMFQ trajectories. Mean SMFQ differences at ages 12, 14, 16, 18, 20, 22 and 24 are calculated between trajectories. ■ indicates age comparison for no trauma. ▲ indicates age comparison for yes trauma. * indicates $p < .001$.



(b) Adjusted association between number of trauma types (between 5-10 Years) and SMFQ Trajectories

Figure 7.2: Adjusted association between childhood traumas and trajectories of depressive symptoms. SMFQ: Short Mood and Feelings Questionnaire

7.5.4 Association between the number of types of trauma and trajectories of depressive symptoms

As shown in figure 7.2.b, there was an exposure-response relationship between the number of types of traumas (between ages 5-10) and later trajectories of depressive symptoms, with a tendency for more traumatic experiences in childhood to be associated with steeper trajectories of depressive symptoms. All four trajectories increased throughout adolescence and began to decrease from about the age of 18 and all trajectories again began to rise from the age of about 22. These differences between trajectories were mainly characterised by individuals who experienced no trauma having a lower intercept score at age 16 (β = 5.18, SE= 0.11 [95% CI: 4.97, 5.39]) compared to individuals with one trauma (β = 5.9, SE= 0.15 [95% CI: 5.61, 6.18]; $p^{DIFF} < .001$), two traumas (β = 6.87, SE= 0.23 [95% CI: 6.43, 7.32]; $p^{DIFF} < .001$) and three or more types of traumas (β = 8.81, SE= 0.35 [95% CI: 8.12, 9.49]; $p^{DIFF} < .001$). There was a weak association between individuals exposed to two traumas and the linear age term (β = 0.43, SE= 0.06 [95% CI: 0.33, 0.54]), compared to non-trauma exposed individuals (β = 0.32, SE= 0.02 [95% CI: 0.28, 0.36]; $p^{DIFF} = .05$), which suggested that individuals exposed to two traumatic experiences may have higher linear growth. There were no associations between the remaining age terms and the non-trauma, one trauma and two traumas exposed individuals ($ps^{DIFF} = .13$), suggesting that overall growth of the trajectories did not differ substantially between no trauma and the one/two traumas trajectories. There were also associations between individuals exposed to three or more types of traumatic experiences and the linear (β = 0.51, SE= 0.09 [95% CI: 0.34, 0.67]), quadratic (β = -0.2, SE= 0.03 [95% CI: -0.26, -0.15]), cubic (β = -0.009, SE= 0.002 [95% CI: -0.01, -0.005]) and quartic age terms (β = 0.004, SE= 0.001 [95% CI: 0.003, 0.005]), compared to the linear (β = 0.32, SE= 0.02 [95% CI: 0.32, 0.36]; $p^{DIFF} = .03$), quadratic (β = -0.1, SE= 0.01 [95% CI: -0.11, -0.08]; $p^{DIFF} = <.001$), cubic (β = -0.004, SE= 0.001 [95% CI: -0.01, -0.003]; $p^{DIFF} = .05$) and quartic age terms (β = 0.002, SE= 0.0001 [95% CI: 0.001, 0.002]; $p^{DIFF} = <.001$) for those individuals who were not exposed to any trauma respectively. This suggested that individuals exposed to three or more types of traumas had less favourable trajectories that had a higher rate of change compared to the non-trauma exposed group. Full estimates are shown in table 7.3.

	Direct Model Output			Alternative Parametrisation		
Parameter	**Estimate (95% CIs)**	**Std. Error**	***p* value**	**Estimate (95% CIs)**	**Std. Error**	***p* value**
No Traumas Intercept	5.18 [4.97, 5.39]	0.11	<.001	5.18 [4.97, 5.39]	0.11	<.001
No Traumas x Age	0.32 [0.28, 0.36]	0.02	<.001	0.32 [0.28, 0.36]	0.02	<.001
No Traumas x Age2	-0.10 [-0.11, -0.08]	0.01	<.001	-0.10 [-0.11, -0.08]	0.01	<.001
No Traumas x Age3	-0.004 [-0.01, -0.003]	0.001	<.001	-0.004 [-0.01, -0.003]	0.001	<.001
No Traumas x Age4	0.002 [0.001, 0.002]	0.0001	<.001	0.002 [0.001, 0.002]	0.0001	<.001
1 Trauma Intercept	0.72 [0.43, 1.02]	0.15	<.001	5.90 [5.61, 6.18]	0.15	<.001
1 Trauma x Age	0.02 [-0.06, 0.09]	0.04	0.64	0.34 [0.28, 0.4]	0.04	0.64
1 Trauma x Age2	0.02 [-0.01, 0.04]	0.01	0.13	-0.08 [-0.1, -0.06]	0.01	0.13
1 Trauma x Age3	-0.001 [-0.003, 0.001]	0.001	0.5	-0.005 [-0.007, -0.004]	0.001	0.5
1 Trauma x Age4	-0.0003 [-0.001, 0.0002]	0.0002	0.22	0.001 [0.001, 0.002]	0.0002	0.22
2 Traumas Intercept	1.70 [1.24, 2.15]	0.23	<.001	6.87 [6.43, 7.32]	0.23	<.001
2 Traumas x Age	0.11 [-0.0001, 0.23]	0.06	0.05	0.43 [0.33, 0.54]	0.06	0.05
2 Traumas x Age2	-0.01 [-0.04, 0.03]	0.02	0.6	-0.10 [-0.14, -0.07]	0.02	0.6
2 Traumas x Age3	-0.002 [-0.01, 0.001]	0.002	0.13	-0.007 [-0.01, -0.004]	0.002	0.13
2 Traumas x Age4	0.0004 [-0.0003, 0.001]	0.0004	0.28	0.002 [0.001, 0.003]	0.0004	0.28
3+ Traumas Intercept	3.63 [2.94, 4.32]	0.35	<.001	8.81 [8.12, 9.49]	0.35	<.001
3+ Traumas x Age	0.19 [0.02, 0.36]	0.09	0.03	0.51 [0.34, 0.67]	0.09	0.03
3+ Traumas x Age2	-0.11 [-0.16, -0.06]	0.03	<.001	-0.20 [-0.26, -0.15]	0.03	<.001
3+ Traumas x Age3	-0.005 [-0.01, -0.0001]	0.002	0.05	-0.009 [-0.01, -0.005]	0.002	0.05
3+ Traumas x Age4	0.002 [0.001, 0.003]	0.001	<.001	0.004 [0.003, 0.005]	0.001	<.001
Deviance	189944.36					

Table 7.3: Adjusted associations between number of traumas (5-10 Years) and SMFQ trajectories (n=6,711). The no traumas variable should be viewed as the reference category as the number of traumas were coded as dummy variable (0/1/2/3). The intercept coefficient (and the coefficients for the subsequent age terms) for an individual with 3+ traumas is the no trauma intercept + 3+ traumas intercept. The Alternative Parametrisation results can therefore be thought of as the completed results. The adjusted analysis included child sex, maternal postnatal depression, maternal education and social economic status at birth and parity.

7.5.5 Comparing depressive symptom scores at different ages

To aid the interpretation of this analysis I compared predicted depressive symptoms scores at various ages throughout adolescence and young adulthood. I then examined whether these symptoms scores differed by the varying trajectories. To correct for multiple hypothesis testing, I used a Bonferroni adjustment of 0.001[2] to estimate corrected main effects between these differences. As shown in table 7.4, the predicted depressive symptoms scores at all ages were higher for individuals exposed to any trauma, compared to those who experienced no trauma ($ps^{DIFF} = <.001$). The largest difference between these two trajectories occurred at age 20 ($\beta = 1.37$, SE= 0.16, $p^{DIFF} = <.001$), which corresponded to a 5.27%[3] difference in depressive symptoms.

Results were comparable for the analysis on the number of traumas with individuals with more types of traumas having greater depressive symptoms score differences compared to those who had experienced no trauma as shown in table 7.5. However, there was no difference in predicted depressive symptoms at age 24 between the no trauma trajectory and those with 1 trauma ($\beta = 0.7$, SE= 0.23, $p^{DIFF} = .003$ [Bonferroni adjusted]). Likewise, there were no differences between symptom scores for individuals in the one trauma trajectory, and those in the two traumas trajectory at ages 12, 14 and 22 ($ps^{DIFF} > 0.002$ [Bonferroni adjusted]), and the one trauma trajectory and the three or more trauma trajectory at ages 12 and 22 ($ps^{DIFF} > 0.002$ [Bonferroni adjusted]). There were no differences in symptoms scores between the two traumas trajectory and the three of more trauma trajectory at ages 12, 20, 22 and 24 ($ps^{DIFF} > 0.016$ [Bonferroni adjusted]). The largest difference between the trajectories occurred between the no trauma trajectory and three or more traumas trajectory at age 18 ($\beta = 3.67$, SE= 0.38, $p^{DIFF} = <.001$), which corresponded to a 14% difference in depressive symptoms.

[2]The Bonferroni adjustment was calculated by assuming an alpha level of 0.05. I ran 49 statistical comparisons. Thus, the adjusted Bonferroni corrected level was calculated by 0.05/49 = 0.001. Thus I only declared comparisons with p-values less than 0.001 as significant at the 5% level.

[3]The % difference in depressive symptoms was calculated by taking the predicted difference score (e.g., 1.37) and dividing it by the total maximum depressive symptoms score of 26 (1.37/26=5.27).

No Trauma VS Any Traumas	Age 12	Age 14	Age 16	Age 18	Age 20	Age 22	Age 24
Predicted No Trauma DS Score	2.90 (0.09)	3.89 (0.09)	5.17 (0.11)	5.43 (0.11)	5.20 (0.12)	4.88 (0.13)	5.73 (0.14)
Predicted Any Traumas DS Score	4.03 (0.10)	5.00 (0.11)	6.40 (0.13)	6.73 (0.13)	6.57 (0.14)	6.24 (0.15)	7.03 (0.17)
Difference, *p* value	1.12 (0.10), <.001	1.11 (0.10), <.001	1.23 (0.13), <.001	1.30 (0.14), <.001	1.37 (0.16), <.001	1.36 (0.17), <.001	1.30 (0.20), <.001
SMFQ % Difference	4.31	4.27	4.73	5	5.27	5.23	5
No Traumas VS 1/2/3+ Traumas							
Predicted 1 Trauma DS Score	3.86 (0.11)	4.69 (0.12)	5.90 (0.13)	6.22 (0.15)	6.13 (0.17)	5.88 (0.18)	6.43 (0.21)
Difference, *p* value	0.95 (0.11), <.001	0.79 (0.12), <.001	0.72 (0.15), <.001	0.78 (0.16), <.001	0.93 (0.18), <.001	0.99 (0.20), <.001	0.70 (0.23), =.003*
SMFQ % Difference	3.65	3.04	2.77	3	3.58	3.81	2.69
Predicted 2 Traumas DS Score	4.27 (0.17)	5.30 (0.18)	6.87 (0.23)	7.27 (0.24)	7.14 (0.26)	6.89 (0.33)	7.99 (0.21)
Difference, *p* value	1.37 (0.17), <.001	1.40 (0.18), <.001	1.70 (0.23), <.001	1.84 (0.25), <.001	1.94 (0.27), <.001	2.00 (0.29), <.001	2.25 (0.35), <.001
SMFQ % Difference	5.27	5.38	6.54	7.08	7.46	7.69	8.65
Predicted 3+Traumas DS Score	4.67 (0.26)	6.50 (0.28)	8.81 (0.35)	9.10 (0.37)	8.26 (0.40)	7.24 (0.42)	8.71 (0.49)
Difference, *p* value	1.77 (0.26), <.001	2.61 (0.28), <.001	3.63 (0.35), <.001	3.67 (0.38), <.001	3.06 (0.27), <.001	2.36 (0.43), <.001	2.97 (0.50), <.001
SMFQ % Difference	6.81	10.04	13.96	14.12	11.77	9.08	11.42

Table 7.4: Comparisons between no trauma trajectories and 1) any trauma trajectories 2) number of types of traumas trajectories at various ages. DS: Depressive symptoms. SMFQ: Short mood and feelings questionnaire. Predicted mean depressive symptom scores calculated at various ages for each trajectory (standard errors are given in parenthesis). All analysis was Bonferroni corrected (an alpha level of 0.05 divided by the number of statistical comparisons (49) is therefore 0.05/49= 0.001) to allow for multiple hypothesis testing. * denotes results were not significant at the Bonferroni adjusted level.

1 Trauma VS 2/3+ Traumas	**Age 12**	**Age 14**	**Age 16**	**Age 18**	**Age 20**	**Age 22**	**Age 24**
Predicted 1 Trauma DS Score	3.86 (0.11)	4.69 (0.12)	5.90 (0.13)	6.22 (0.15)	6.13 (0.17)	5.88 (0.18)	6.43 (0.21)
Predicted 2 Traumas DS Score	4.27 (0.17)	5.30 (0.18)	6.87 (0.23)	7.27 (0.24)	7.14 (0.26)	6.89 (0.33)	7.99 (0.21)
Difference, *p* value	0.41 (0.18), =.025*	0.61 (0.2), =.002*	0.97 (0.25), <.001	1.05 (0.27), <.001	1.01 (0.29), =.001	1.01 (0.32), =.002*	1.56 (0.38), <.001
SMFQ % Difference	1.58	2.35	3.73	4.04	3.88	3.88	6
Predicted 3+Traumas DS Score	4.67 (0.26)	6.50 (0.28)	8.81 (0.35)	9.10 (0.37)	8.26 (0.4)	7.24 (0.42)	8.71 (0.49)
Difference, *p* value	0.82 (0.27), =.002*	1.82 (0.29), <.001	2.91 (0.37), <.001	2.89 (0.39), <.001	2.13 (0.42), <.001	1.36 (0.45), =.002*	2.28 (0.53), <.001
SMFQ % Difference	3.15	7	11.19	11.12	8.19	5.23	8.77
2 Trauma VS 3+ Traumas							
Predicted 2 Traumas DS Score	4.27 (0.17)	5.30 (0.18)	6.87 (0.23)	7.27 (0.24)	7.14 (0.26)	6.89 (0.33)	7.99 (0.21)
Predicted 3+ Traumas DS Score	4.67 (0.26)	6.50 (0.28)	8.81 (0.35)	9.10 (0.37)	8.26 (0.4)	7.24 (0.42)	8.71 (0.49)
Difference, *p* value	0.40 (0.3), =.176*	1.21 (0.32), <.001	1.94 (0.41), <.001	1.83 (0.43), <.001	1.12 (0.47), =.016*	0.35 (0.5), =.478*	0.72 (0.59), =.221*
SMFQ % Difference	1.54	4.65	7.46	7.04	4.31	1.35	2.77

Table 7.5: Comparisons between number of types of traumas trajectories at various ages. DS: Depressive symptoms. SMFQ: Short mood and feelings questionnaire. Predicted mean depressive symptom scores calculated at various ages for each trajectory (standard errors are given in parenthesis). All analysis was Bonferroni corrected (an alpha level of 0.05 divided by the number of statistical comparisons (49) is therefore 0.05/49= 0.001) to allow for multiple hypothesis testing. * denotes results were not significant at the Bonferroni adjusted level.

7.6 Discussion

7.6.1 Main findings

I examined the association between childhood trauma and trajectories of depressive symptoms between the ages of 11 and 24 years. I also examined how the number of types of trauma exposure reported during mid-childhood may be associated with higher trajectories of depressive symptoms. One of the main goals was to convey these results in a more interpretable manner that might be beneficial for researchers, clinicians and policy makers. Previous research tends to just display the coefficients from a model, thus making it difficult to interpret results that are non-linear over time. I have provided a framework which easily transforms direct model output into more interpretable coefficients that can be compared across multiple stages of development. Figure 7.2.a demonstrates the utility of this approach. The use of this framework quantifies how different population averaged trajectories vary between each other at varying times (i.e., how no trauma individuals differ from exposed to trauma individuals at age 12 or age 18 etc). I hope that future research will utilise this approach for other trajectory comparisons in the hope of developing and improving treatments and interventions.

Exposure to childhood trauma was strongly associated with a steeper trajectory of depressive symptoms. As well as having higher predicted depressive symptoms scores at age 16, predicted symptoms scores were also higher between the ages of 12 and 24. However, the growth or rate of change did not change substantively depending on exposure to trauma. Importantly, the analysis on the number of types of traumas revealed an exposure-relationship response which demonstrated that a greater number of the types of traumatic experiences in childhood was associated with less favourable trajectories. Whilst the overall rate of change did not differ substantially between those not exposed to trauma and those who reported either one or two types of trauma exposure, individuals exposed to three or more trauma types (i.e., those who are polyvictimised) had a substantively higher rate of change compared to non-exposed individuals. Specifically, polyvictimised individuals had an increased rate of depressive symptoms throughout adolescence, which suggests that depressive symptoms were getting worse more rapidly compared to individuals who did not report exposure to trauma. Importantly, I also observed that depressive symptoms scores were higher at almost every two-year interval for the non-exposed individuals compared to those with exposure to one, two or three or more types of trauma. The greatest difference occurred between the no trauma trajectory and the three or more traumas trajectory at age 18 (corresponding to nearly a 4 point or 14% difference in depressive symptoms).

These findings advance the results from chapter 5, and support previous research examining the effects of trauma and negative life experiences on later trajectories of depressive symptoms [104, 185–187], and the number of traumatic events on higher trajectories [34]. These findings are consistent with additional research that suggests that childhood trauma has lasting and persistent impact on later depressive symptoms [182, 183] and efforts should be made to prevent traumatic experiences occurring in childhood and support those individuals who are exposed to trauma [184]. This research highlights that those most at risk (i.e., polyvictimised in childhood) have substantially less favourable trajectories of depressive symptoms and efforts should be made to support this at-risk group, potentially through community and individual-level interventions to mitigate or prevent the risk of adverse mental health outcomes post-trauma and throughout adolescence. These results also suggest that polyvictimised individuals have depressive symptoms that get worse at much faster rate and have higher symptoms for longer. This suggests there are continuing effects of early childhood trauma on depressive symptoms that manifest at a faster rate (meaning they could be easily missed in screening) and are maintained/heightened throughout adolescence (meaning they may be hard to continually treat).

There are several mechanisms, both psychological and biological, that have been considered to contribute to the pathway from exposure to traumatic experiences to the development of depression. Findings of the association between exposure to trauma and the trajectory of depressive symptoms may inform theoretical frameworks of these mechanisms. Trauma in early life may have lasting effects on the risk of depression due to its impact during development, and as such reduces the ability to build resilience in adolescence which results in an increased risk of greater depressive symptoms later in life [24, 182, 191]. Chronic exposure to childhood trauma is associated with repeated victimisation and psychological distress in adolescence [188], and a range of negative functional outcomes in adulthood [182]. Previous research has also found that extreme stress during childhood and adolescence may have stronger or longer lasting effects on the HPA axis compared to trauma exposure in adulthood [192], and is considered a key mediator in the relationship between trauma and negative mental health outcomes [193, 194]. Findings for increased risk of depressive symptoms from exposure to trauma over the course of adolescence is consistent with evidence of sustained dopamine dysregulation from trauma exposure during early life [192].

7.6.2 Considerations

I have transformed the direct model output into two potentially more helpful frameworks which better highlight results and I consider this one of the key contributions of this work. The first is to transform the original model coefficients into a calculated set of alternative model framework: the "Alternative Parametrisation". This simply adds the baseline intercept and age terms onto the additional groups giving a clearer idea of what depressive symptoms scores are at the intercept age and how they change over a one-year period. However, as the trajectories are non-linear and have multiple age terms, even this can be challenging to interpret, so the second approach is to create predicted depressive symptoms scores at various ages for different population averaged trajectories and to compare them with degrees of uncertainty. This takes into account the non-linearity of the age terms and represents an easy way to interpret the coefficients from the model. Both these methods could improve interpretation from the direct model output and are important to highlight as it is important to know the coefficients for change over time, not just what the scores are at the intercept. Such analysis could be useful for individuals without statistical backgrounds, and it is much easier to interpret a predicted mean difference in symptoms at a particular age, rather than interpreting complex non-linear and contrasting coefficients (e.g., interpreting a positive linear age term but negative quadratic and positive cubic terms). Interpreting these coefficients in isolation is often not practical, but the framework presented in tables 7.2, 7.3, 7.4, 7.5 and figure 7.2.a could aid in the interpretation of complex results into clinical practise and treatment. These results should be used to help interpretation with illustrations and qualitative descriptions of the trajectories.

However, there are certain considerations that must be made. Firstly, in this analysis, I chose to use multilevel growth-curve models. Alternative analysis could have used a growth mixture modelling or latent class approach to derive multiple sub-population trajectories and then compared depressive symptom scores at various ages between differing sub-population trajectories (i.e., differences in depression at age 12 between a stable low, increasing and decreasing trajectory). I chose to use a population-averaged approach with quartic polynomials in order to quantify the population averaged rate of change of depressive symptoms associated with exposure to varying degrees of trauma. However, higher order polynomials may constrict the data to take a quartic shape, thus giving estimates that are extrapolated beyond the data. This problem would also be present in the growth mixture and latent class approach. It could be possible to use other functions of time in place of higher order polynomials such as splines and fractional polynomials [61]. However, extrapolation beyond the data is still an issue with these models. Thus, a safer option to account

for extrapolation would be to refrain from computing estimates close to the tails of the trajectory. This would avoid calculating nonsensical estimates that are beyond the range of the data.

A second consideration regards the number of tests that could be run in the framework presented here. As shown in tables 7.4 and 7.5, I ran multiple comparisons between the no trauma and yes trauma trajectories, and with the no trauma and number of trauma trajectories, resulting in 49 statistical comparisons. Whilst it is important to compare these multiple ages, one concern is that by running multiple sets of analysis, the chances of obtaining a type one error increase (i.e., reporting a sample mean difference to be significant when there is not mean difference in the population: a chance result). Alternatively, such methods may also facilitate research that searches for "statistically significant" differences. This is not the point of such analysis and I advocate the use of Bonferroni adjusted comparisons, or false discovery rates (FDR) to minimise the impact of both scenarios.

7.6.3 Limitations and future research

Attrition plays a part in any longitudinal study. Missing data could be biasing these results. Previous analysis using similar methods has shown that when using multiple methods for dealing with missing data, the estimates do not change substantively [130]. To account for this missing data, I used full information maximum likelihood (FIML) which makes a missing at random (MAR) assumption. However, even though I used this approach to account for missing data, I cannot fully rule out the effect of missing data on these results. One alternative approach would be to use multiple imputation where auxiliary variables can be introduced into the imputation model to make the MAR assumption more credible

Additionally, I only examined childhood trauma between the ages of 5 and 10 years old. There may be varying effects for traumas at earlier or later ages that could be investigated further. However, this was beyond the scope of this analysis and would likely require advanced modelling techniques, in order to approximately capture the time-varying element of childhood trauma. For instance, childhood trauma may cause depression, but there may also be reverse-causal effects from depressive symptoms on the risk of childhood trauma. Future models should take such modelling into account when examining the longitudinal relationship between childhood trauma and depression. Future research should also consider the timing and accumulation of exposures as these are important for later depression [124, 195]. For example, those who have exposure to multiple instances of trauma over consecutive periods of development may be at the greatest risk, but research has yet

to explore this.

Also, many of the childhood trauma items were parent-reported, which may be subject to report bias. However, sensitivity analyses using this data has found little difference in parent-child reports for trauma [189]. The measure of exposure frequency used in the analysis is based on the number of different types of trauma reported, which is only an approximate measure of how chronic trauma exposure is during the age period. There may be variation in the frequency of a single type of trauma exposure and its severity that this analysis is unable to account for. This analysis also assumes that there is an equal effect of each trauma type on the risk of depression, which may not be the case. These analyses were not the primary focus of this analysis, however, future research should look to explore the impact of different types of trauma and their associations with later depression as this may help identify at risk individuals, who could be targeted for interventions and treatment.

Previous research has also shown that sex differences in child trauma and depression may exist , and evidence suggests that stressful life events increase female trajectories of depressive symptoms, but not males [97, 107]. However, the opposite effect has also been observed in another study [74]. Sex differences were beyond the scope of this analysis as I was initially interested in presenting a model interpretation framework for trajectories analysis with a binary and then categorical variable. However, this methodology could be extended to run a three-way interaction between sex, exposure to trauma and varying trajectories of depressive symptoms.

7.7 Conclusions

In conclusion, exposure to childhood trauma was associated with less favourable trajectories of depressive symptoms. Further to this, there was an exposure-response relationship with the number of reported types of trauma, with individuals exposed to 3 or more childhood traumas having substantially higher trajectories of depressive symptoms. These results suggest that polyvictimised children should be considered at higher risk of depression during adolescence, which could inform intervention approaches. I have also provided an alternative model interpretation framework for examining and comparing trajectories of depressive symptoms, which shows depressive symptoms scores at different ages for different trajectories. This framework could be more interpretable for researchers, clinicians and policy workers, which could eventually aid in the translation of such findings into preventative interventions and treatments.

7.8 Chapter summary

This chapter has shown that childhood trauma and in particular, the number of childhood traumas are strong risk factors for higher population averaged trajectories of depressive symptoms. This chapter extends the findings from chapters 4, 5 and 6 and primarily addresses the second research objective by showing the association between childhood trauma and trajectories of depressive symptoms. This chapter also addresses the fourth research objective by translating the estimates from the complex trajectories model into simpler results that can be easily interpreted using an "alternative model parametrisation". In doing so, this chapter has also addressed the third research objective by highlighting several critical points of trajectories where childhood trauma could be having its greatest effect on later adolescent depressive symptoms. These points highlight when childhood trauma is likely to have its greatest effect which could be used to guide support and interventions. Importantly, I have advanced the findings from chapter 5 that looked at bullying and have shown that the number of types of traumatic experiences (i.e., an accumulation of traumatic events) are an important risk factor for trajectories of depressive symptoms.In the next chapter, I build upon this work, and the findings from chapters 4,5 and 6 to show how genetic risk for depressive symptoms is associated with trajectories of depressive symptoms and if the population-averaged trajectories approach can used to determine when genetic risk begins to manifest during adolescence and when it is having its greatest effect.

Chapter 8

Association Between Polygenic Risk and Trajectories of Depressive Symptoms

8.1 Chapter outline

This final research chapter is the culmination of chapters 4, 5, 6 and 7, and aims to demonstrate how genetic risk for depressive symptoms is associated with trajectories of depressive symptoms. Chapter 5 showed that genetic risk for depressive symptoms was associated with the two more severe trajectories: the childhood persistent and early adult-onset trajectories, suggesting that more severe and pervasive trajectories of depressive mood may have a genetic basis. In this chapter, I use the population-averaged trajectories derived in chapter 4, and the alternative model parametrisation used in chapter 7 to explore the association between genetic risk and trajectories of depressive symptoms in greater detail. Using the methods highlighted in chapters 6 and 7, this chapter determines when genetic risk begins to manifest and when it is having its greatest effect on depressive symptoms.

This chapter primarily addresses the second research objective: "how are genetic and environmental risk factors differentially associated with varying trajectories of depressive symptoms?". But much like chapter 7, this chapter also addresses the third research objective: "are there critical points of trajectories of depressive symptoms which tell us more about how and when depression changes across adolescence?" and the fourth research objective: "can the results from trajectory models be simplified to aid in the interpretation and translation of findings?". Part of this chapter was submitted as a manuscript to Psychological Medicine. All supplementary materials are provided in appendix 8.

Kwong, A. S. F., Morris, T. T., Pearson, R. M., Rice, F., Stergiakouli, E., Tilling, K. (Submitted to Psychological Medicine). Association Between Genetic Liability and Trajectories of Depressive Symptoms.

8.2 Chapter abstract

Adolescence marks a period where depression will commonly onset and previous research using twin studies has suggested that genetic influences play a role in how depression manifests and changes across adolescence. Recent genome-wide association studies have also shown that common genetic variants – often summed into polygenic risk scores (PRS) are also implicated in depression. However, the role of PRS in adolescent depression and changes in adolescent depression is not yet fully understood. The aim of this chapter was to examine the association between a PRS for depressive symptoms and depressive symptoms across adolescence and young adulthood, and how polygenic risk may influence changes in depressive symptoms using two methods: cross-sectional analysis and growth curve modelling.

I used data from over 7000 participants of the Avon Longitudinal Study of Parents and Children (ALSPAC) to examine associations between a depressive symptoms (PRS), and depressive symptoms measured on nine occasions between the ages of 10 and 24 years using the short mood and feelings questionnaire. I examined cross-sectional associations at each age and trajectories of depressive symptoms in a repeated measures framework using growth curve analysis.

The PRS was associated with depressive symptoms throughout adolescence and young adulthood in both cross-sectional and longitudinal analyses, though associations were stronger in the longitudinal analyses. Additionally, longitudinal analyses provided additional insights, demonstrating that individuals with a higher PRS for depressive symptoms were associated with higher trajectories of depressive symptoms that were characterised by greater depressive symptoms scores at age 16 and a steeper increase in depressive symptoms over time.

These results provide further support for the role of common variants in the onset and severity of adolescent depressive symptoms and how they change over time – most notably that a PRS for depressive symptoms is associated with how depressive symptoms change across development. Repeated measures models may provide additional insights that could be used to help identify potential pathways in the onset and maintenance of depression.

8.3 Introduction

Adolescence marks a period where depression will often onset [3, 16, 17], with depression during this stage of development associated with a number of psychiatric and social impairments in later life [19, 20, 196]. Understanding the nature of adolescent depression is important for developing treatments and interventions that could help reduce these impairments.

Depression has a complex and multifactorial aetiology [197], comprised of both environmental and genetic contributions [151]. With regards to genetic influences, twin studies have estimated that the heritability of depression is between 31% - 42% [198], suggesting there is a sizable genetic component. Twin studies on childhood and adolescent depression have also suggested that depression is partly heritable with estimates similar to that of adult depression around 40% [199]. However, this estimate varies between studies and can range between 11% - 72% [200]. Twin studies have also shown that genetic influences may play a role in how depressive mood changes across adolescence [28], and in particular that genetic influences may increase throughout development [146, 201]. A recent study of American twins found that additive genetic effects explained a greater amount of variance in depression around mid-to late-adolescence than early childhood [202]. However, a separate study found that twin estimated heritability of depression decreased across childhood, and was relatively stable throughout adolescence [203]. Evidence from molecular studies has also shown inconsistent heritability throughout adolescence using single nucleotide polymorphisms (SNPs), with heritability ranging between 2% and 17% [180]. Interestingly, Sallis and colleagues identified a peak in heritability at age 13, which declined thereafter. Using longitudinal data to measure genetic influences of depression could be useful for examining pathways towards depression and examining when genetic effects are likely to have the greatest effects on depression across periods of development.

Recent advances in large scale molecular studies (i.e., genome-wide association studies [GWAS]) have provided evidence that common genetic variation is also likely to play an important role in depression, with SNP based heritability though to explain about 9% of the variation in depression [9, 122, 123]. GWAS have also demonstrated that depression is polygenic, with many genetic variants or SNPs each having a small effect [121]. Polygenic risk scores (PRS), which sum the number of "risk" variants that an individual possesses for a trait [204], can be used as an indicator of an individual's genetic liability to depression. PRS for depression explains up to about 3.2% of the variation in depression in adult populations [122], yet this approach has yet to be fully explored in younger populations, particularly

with regards to adolescent depression and changes in adolescent depression.

Recent research on children and adolescents has found that a PRS taken from a large GWAS of major depressive disorder (MDD) in adults was associated with both child and adolescent depression in clinical and population cohorts [205]. Halldorsdottir and colleagues found that the PRS predicted up to 5% of variation in case control status, and up to 0.4% of the variance in a population cohort. Likewise, two recent studies have shown that PRS taken from GWAS of depression and depressive symptoms in adult populations are associated with developmental trajectories that are characteristic of the onset of adolescent depression [87], as well as a trajectory that reflects chronic depressive symptoms throughout adolescence and young adulthood, as shown in chapter 5. Together, these studies highlight that polygenic risk is likely to play a role in the development and maintenance of adolescent depression. However, as some studies have only assessed depression across parts of development (i.e., ages 12-17) or at single occasions in cross-sectional designs, it is not clear when polygenic risk is having the greatest contribution to depression in adolescence, or if polygenic risk plays a role in how depression changes across development. Examining if greater polygenic risk manifests differentially over time, and if it is associated with change over time could enhance our understanding of the nature of adolescent depression and help identify potential pathways in the onset of depression.

There is evidence that PRS are associated with changes across childhood and adolescence for other traits such as height [206] and BMI [207, 208]. These studies have all used a repeated measures framework (i.e., to estimate trajectories or growth curve models) to examine genetic influences for changes in a trait. Evidence suggests that using a repeated measures framework such as growth curve modelling may help improve the statistical power of genetic analysis [120]. For example, measurement error and low power are problems in genomic analysis as genetic effects tend to be small in magnitude and require large sample sizes with precision to detect true effects [209]. Likewise, variation in the reported genetic component for depression (i.e., heritability) may be partially a result of measurement error in longitudinal studies that have multiple assessments [199]. However, a longitudinal approach which uses repeated measures may reduce measurement error and minimise noise by increasing statistical power as there are multiple occasions included in the analysis, rather than just one occasion [157]. Multiple measurements also maximise the number of participant responses and may obtain a more precise estimate of an individual's "true" latent trait score as the assessment is repeated over time, and not just at one occasion. It is also possible to reduce the burden for multiple testing in a growth curve setting as the number of multiple comparisons are reduced [210]. Repeated measures analysis, in particular growth curve modelling, may provide an advantage

to traditional cross-sectional analysis and also quantify how a trait changes over time, which in this context could help further explain the role of genetics in changes to adolescent depression over time.

The aim of this chapter was to examine how a PRS for depressive symptoms was associated with depressive symptoms, and changes in depressive symptoms across adolescence. Evidence suggests that depression should be viewed on a continuum [8, 9], as depressive symptoms are strongly associated with depression [10, 12], and elevated depressive symptoms are associated with a host of adverse outcomes similar to depression [143, 144]. I conducted several analyses: 1) I used a PRS taken from a recent GWAS of depressive symptoms [156], and examined associations at nine separate occasions in a UK based population cohort between the ages of 10 and 24 years old (cross-sectional analysis). 2) I then used growth curve modelling to construct trajectories of depressive symptoms in the same cohort and examined how the PRS for depressive symptoms was associated with change in depressive symptoms throughout adolescent development. 3) finally, I then examined if a higher PRS was associated with differences in depressive symptoms scores across this developmental period.

8.4 Methods

8.4.1 Sample

Data were taken from the Avon Longitudinal Study of Parents and Children (ALSPAC), as described in chapter 3.

8.4.2 Depressive Symptoms

Depressive symptoms were measured on nine occasions between ages 10 and 24 using the short mood and feelings questionnaire (SMFQ) [129]. See chapter 3 for specific details and table 8.1.

8.4.3 Polygenic risk score for depressive symptoms

The PRS for depressive symptoms was created in PRSice [155], using summary statistics from a recent genome wide association study (GWAS) of depressive symptoms on 161,460 individuals [156],as descibed in chapter 5. The PRS was created by weighting the effect sizes of 120,422 single nucleotide polymorphisms (SNPs) asso-

ciated with depression symptoms from the initial GWAS at eight p value thresholds (as $5x10^{-08}$, $5x10^{-07}$, $5x10^{-06}$, $5x10^{-05}$, $5x10^{-04}$, $5x10^{-03}$, $5x10^{-02}$ and $5x10^{-01}$). The PRS was standardised to have a mean of 0 and a standard deviation of 1, thus a higher PRS represents higher liability to depression symptoms. Further genotyping information is available in chapter 5 and appendix 8.

8.4.4 Statistical analysis

For the cross-sectional analysis, linear regression analysis was used to examine the association between depressive symptoms and the PRS at each of the nine occasions. P values were corrected for false discovery rate (FDR) due to the number of statistical tests (eight PRS thresholds x nine depressive symptoms occasions [72 tests]). Bootstrapping, with 1000 repetitions was used to calculate confidence intervals for R2 (the amount of variance explained by the PRS).

For the repeated measures analysis, trajectories of depressive symptoms were estimated using multilevel growth-curve modelling [59, 131], as described in chapter 4. Briefly, I again used a multilevel quartic growth-curve polynomial model which contained five key parameters: the intercept, the linear age term, the quadratic age term, the cubic age term and the quartic age term. To examine how the PRS was associated with changes in the growth curve model, I included a main effect of the standardised PRS and an interaction of the PRS with the intercept and each of the fixed-effects age polynomial terms (i.e., the linear, quadratic, cubic and quartic age terms). Age was grand-mean centred to 16.53 years (the mean age of all assessments) in order to improve interpretation, since model intercept and intercept variance then correspond to the middle of adolescence [102]. The intercept and four polynomial age terms were allowed to vary randomly across individuals to capture each individual's unique trajectory (i.e., each person had their own intercept and slope). Further information regarding model fit and the model equations can be found in appendix 8.

In order to highlight differences between greater or lower PRS on changes in depressive symptoms, I also created trajectories that were +/- 1 standard deviation (SD), thus resulting in two trajectories (greater risk [+1 SD] vs. lower risk [-1 SD]). I then calculated the predicted depressive symptoms scores at each of the following ages: 10.64, 12.81, 13.83, 16.68, 17.82, 18.64, 21.95, 22.88 and 23.86 (to coincide with the ages at which the SMFQ was assessed at each of the nine occasions), for both the greater and lower PRS trajectories. I then compared the predicted depressive symptoms scores at each of these ages between greater and lower PRS trajectories. Further information on how these were calculated for the trajectories is presented in

the previous chapter and in appendix 7, but briefly the depressive symptoms scores are calculated at each age for the two trajectories (i.e., depressive symptom scores at age 12 for the low PRS and high PRS trajectory). Then using the delta method (which incorporates the estimate, standard errors and confidence intervals), these two scores are then compared to reveal an estimated difference that has measures of certainty and precision.

Finally, I ran negative control analysis between the height PRS and trajectories of depressive symptoms and between the depressive symptoms PRS and height trajectories (see appendix 8 for more details).

All analyses were conducted using Stata 15 (StataCorp, College Station, TX, USA), with trajectories analysis using the user-written runmlwin command [134], which calls the standalone multilevel modelling package MLwiN v3.01. All analyses were adjusted for sex, age (only in the cross-sectional analyses, as the longitudinal analyses adjust for age by default) and the first ten principal components of ancestry.

8.4.5 Missing data

Missing data in the trajectories analysis were handled using full information maximum likelihood estimation (FIML) [211]. Briefly, this assumes that the probability of an individual missing a measure of depressive symptoms does not depend on their underlying depressive symptoms score at that occasion, given their observed depressive symptoms trajectory at other occasions. I included individuals into analysis if they had at least one measurement of depression symptoms in order to maximise power [130]. Previous research on these data has shown that trajectory shapes and characteristics do not vary when comparing individuals with at least one or at least 4 measurements of depressive symptoms as shown in chapter 6.

8.5 Results

8.5.1 Sample characteristics

Of the original 14,901 participants, 9,399 individuals had at least one measurement of depressive symptoms and 7,877 had genotype data that passed quality control, removal of non-Europeans and related samples. For the cross-sectional analysis, data were available for 5,324 individuals with a measurement of depressive symptoms at age 10 and genotype data. However, sample size decreased to 2,737 individuals with both a depression symptoms measurement at age 24 and genotype data. Descriptive

information can be found in table 8.1. For the repeated measures analysis, data were available for 6,305 individuals with at least one measurement of depressive symptoms and genotype data.

Occasion (Total N)	N Without PRS	N With PRS	Mean Age Without PRS	Mean Age With PRS	Mean SMFQ Without PRS	Mean SMFQ With PRS
1 (N = 7,364)	2,040	5,324	10.67 (0.29)	10.64 (0.25)	4.15 (3.55)	4.00 (3.49)
2 (N = 6,716)	1,785	4,931	12.83 (0.24)	12.81 (0.23)	4.05 (3.90)	3.94 (3.84)
3 (N = 6,019)	1,521	4,498	13.85 (0.22)	13.83 (0.21)	4.91 (4.49)	4.92 (4.49)
4 (N = 4,997)	1,470	3,527	16.68 (0.24)	16.68 (0.24)	6.04 (5.66)	5.85 (5.63)
5 (N = 4,497)	1,284	3,213	17.89 (0.45)	17.82 (0.37)	6.79 (5.33)	6.50 (5.21)
6 (N = 3,335)	946	2,389	18.67 (0.49)	18.64 (0.49)	7.05 (6.12)	6.73 (5.85)
7 (N = 3,305)	925	2,380	21.97 (0.53)	21.95 (0.52)	6.05 (5.84)	5.56 (5.46)
8 (N = 3,856)	1,149	2,707	22.92 (0.53)	22.88 (0.51)	6.54 (5.87)	6.07 (5.40)
9 (N = 3,915)	1,178	2,737	23.89 (0.52)	23.86 (0.51)	7.48 (6.38)	6.84 (5.91)

Table 8.1: Descriptives of the SMFQ between those with and without genetic data. PRS: Polygenic Risk Score. Standard deviations are given in (parenthesis).

8.5.2 Association between depressive symptoms polygenic risk score and depressive symptoms using cross-sectional analysis

The depressive symptoms PRS showed weak and inconsistent associations with depressive symptoms using the more stringent thresholds for the PRS such as $5x10^{-08}$, $5x10^{-07}$, $5x10^{-06}$, $5x10^{-05}$ and $5x10^{-04}$, similar to previous analyses [205]. This is likely a result of low power as these thresholds include a small number of variants and explain a small amount of variation. More liberal thresholds have been used when examining the predictive capabilities of PRS [9]. Therefore, the remaining analysis focuses on the more liberal PRS thresholds of 0.005, 0.05 and 0.5. Full estimates are given for all analyses can be found in appendix 8.

The PRS with the strongest association varied according to the occasion (i.e., at what age depressive symptoms were measured). The PRS with a threshold of 0.5 showed the strongest associations between a one standard deviation increase of the PRS and depressive symptoms at age 10.60 (β = 0.129, 95 CIs = 0.034, 0.223, p^{FDR} = 0.026), age 12.80 (β = 0.210, 95 CIs = 0.102, 0.317, p^{FDR} = 0.001), age 13.80 (β = 0.170, 95 CIs = 0.041, 0.299, p^{FDR} = 0.028), age 17.80 (β = 0.413, 95 CIs = 0.236, 0.591, $p^{FDR} = 9.00x10^{-05}$), and age 22.90 (β = 0.456, 95 CIs = 0.253, 0.658, p^{FDR} = 0.001). However, the PRS with a threshold of 0.005 showed the strongest associations between a one standard deviation increase of the PRS and depressive symptoms at age 16.70 (β = 0.349, 95 CIs = 0.170, 0.528, p^{FDR} = 0.001), age 18.70 (β = 0.453, 95 CIs = 0.225, 0.681, p^{FDR} = 0.001), age 21.90 (β = 0.371, 95 CIs = 0.153, 0.590, p^{FDR} = 0.005) and age 23.90 (β = 0.608, 95 CIs = 0.389, 0.828, $p^{FDR} = 2.12x10^{-06}$). Despite the differences in the PRS threshold, effect sizes increased throughout adolescence and into young adulthood (full estimates are given in appendix 8). An example of the association between the PRS and depressive symptoms using the 0.005 threshold can be seen in table 8.2 and figure 8.1.a, along with predicted values for individuals with 1+ SD above for the PRS at each occasion. Additional analyses across multiple thresholds can also be found in appendix 8.

Age	**PRS Beta (95% CIs)**	**FDR *p* Value**	**△R2 (95% CIs)**	**Predicted SMFQ Score (95% CIs)**	**Predicted SMFQ Score with PRS (95% CIs)**
10.67	0.091 (-0.003, 0.185)	0.121	0.07% (0.05%, 0.09%)	4.19 (4.02, 4.37)	4.29 (4.09, 4.48)
12.81	0.145 (0.038, 0.252)	0.024	0.14% (0.11%, 0.17%)	3.47 (3.27, 3.68)	3.62 (3.39, 3.85)
13.83	0.163 (0.034, 0.292)	0.035	0.13% (0.08%, 0.18%)	3.94 (3.69, 4.19)	4.11 (3.83, 4.39)
16.68	0.349 (0.170, 0.528)	0.0009	0.39% (0.35%, 0.43%)	4.19 (3.84, 4.55)	4.54 (4.14, 4.94)
17.82	0.364 (0.186, 0.543)	0.0008	0.48% (0.44%, 0.52%)	5.72 (5.36, 6.07)	6.08 (5.68, 6.48)
18.64	0.453 (0.225, 0.681)	0.0007	0.61% (0.47%, 0.76%)	5.43 (4.96, 5.91)	5.89 (5.36, 6.41)
21.95	0.371 (0.153, 0.590)	0.005	0.47% (0.35%, 0.58%)	4.86 (4.41, 5.31)	5.23 (4.73, 5.73)
22.88	0.427 (0.224, 0.630)	0.002	0.61% (0.47%, 0.77%)	5.2 (4.78, 5.62)	5.63 (5.16, 6.10)
23.86	0.608 (0.389, 0.828)	$2.12\text{x}10^{-06}$	1.07% (0.76%, 1.37%)	5.91 (5.45, 6.36)	6.51 (6.00, 7.02)

Table 8.2: Table 2. Association between the depressive symptoms PRS and depressive symptoms at various across adolescence. PRS: Polygenic Risk Score; FDR: False Discovery Rate. Upper and lower 95% confidence intervals for the beta are given in (parenthesis). Incremental R2 (△R2) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models. The confidence intervals for △R2 were derived using bootstrapping with 1000 repetitions. The average beta and △R2 were calculated by taking the average across all occasions.

8.5.3 Association between depressive symptoms polygenic risk score and trajectories of depressive symptoms

I selected the PRS with threshold of 0.005 for the trajectory analysis because this PRS threshold showed stronger average effect sizes in the cross-sectional analyses (see Figure 1 and Table 1). Therefore, the subsequent trajectory analysis used this threshold score of 0.005, but I conducted sensitivity analysis at other thresholds, which showed almost identical results (see appendix 8).

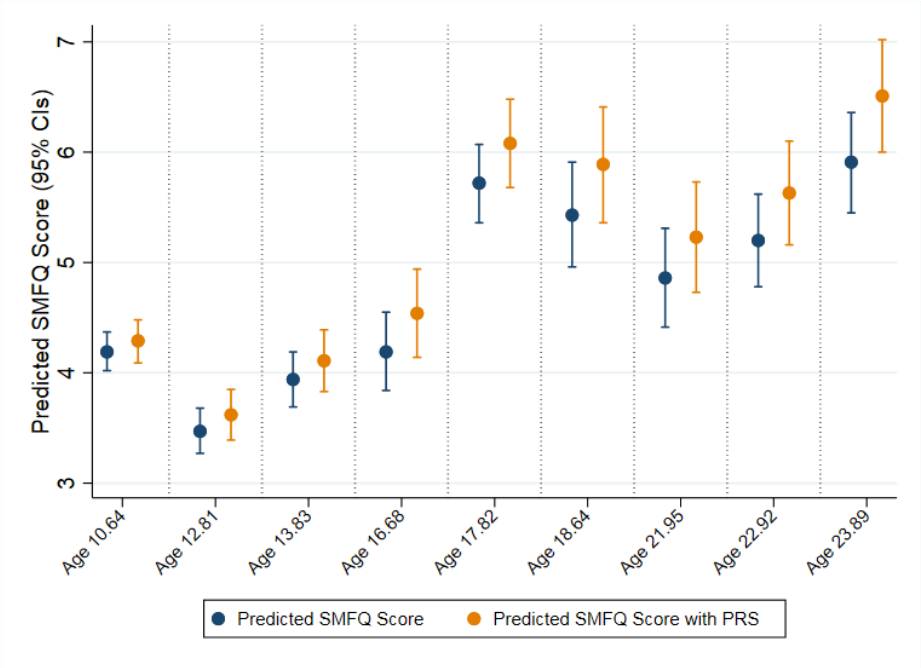
A one standard deviation increase in the depressive symptoms PRS was associated with higher depressive symptoms at the intercept age of 16.53 (β = 0.363, 95 CIs = 0.230, 0.496, p = 8.56x^{-08}). The depressive symptoms PRS also showed evidence for change over time, with a one standard deviation increase in the PRS strongly associated with a linear change in depressive symptoms (β = 0.048, 95 CIs = 0.016, 0.080, p = 0.003). However, a one standard deviation increase in the PRS was not associated with the quadratic, cubic or quartic age terms (see figure 8.2 and appendix 8 for full estimates).

8.5.4 Comparisons between higher and lower genetic risk at various ages

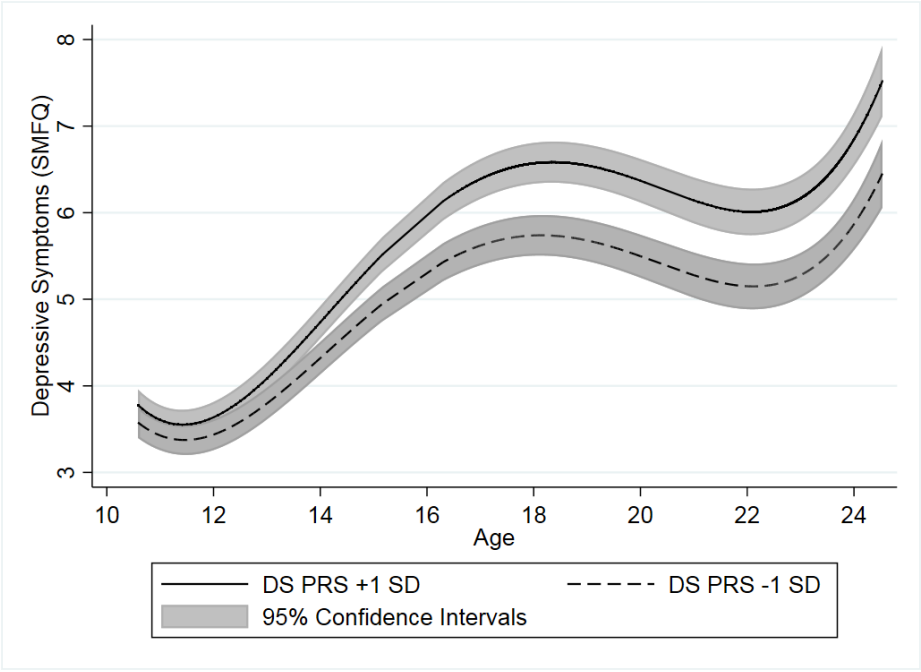
The comparisons between those with higher risk (+1 SD in the PRS) and those with lower risk (-1 SD in the PRS) found evidence that depressive symptoms were higher for those with greater PRS risk across all ages of adolescence and young adulthood ($ps^{FDR} < 0.036$), as shown in table 8.3. The largest difference between these two trajectories was observed at age 24 (β^{DIFF} = 0.96, 95 CIs = 0.59, 1.33, p = 7.43x10^{-07}).

Age	Low DS PRS Estimate (95% CIs)	High DS PRS Estimate (95% CIs)	Difference Estimate (95% CIs)	*p* Value	FDR *p* Value
10.67	3.54 (3.36, 3.71)	3.73 (3.56, 3.91)	0.2 (0.01, 0.38)	0.036	0.036
12.81	3.71 (3.53, 3.89)	3.98 (3.80, 4.16)	0.27 (0.07, 0.46)	0.007	0.008
13.83	4.23 (4.04, 4.41)	4.62 (4.43, 4.80)	0.39 (0.19, 0.59)	0.0001	0.0001
16.68	5.54 (5.32, 5.77)	6.28 (6.06, 6.51)	0.74 (0.47, 1.01)	$6.67\text{x}10^{-85}$	$2.0\text{x}10^{-07}$
17.82	5.73 (5.50, 5.96)	6.55 (6.32, 6.79)	0.82 (0.54, 1.11)	$1.10\text{x}10^{-08}$	$4.95\text{x}10^{-08}$
18.64	5.72 (5.48, 5.95)	6.58 (6.34, 6.81)	0.86 (0.57, 1.15)	$5.67\text{x}10^{-09}$	$5.10\text{x}10^{-08}$
21.95	5.15 (4.89, 5.42)	6.01 (5.74, 6.28)	0.86 (0.52, 1.19)	$4.96\text{x}10^{-07}$	$7.44\text{x}10^{-07}$
22.88	5.24 (4.99, 5.50)	6.12 (5.86, 6.39)	0.88 (0.56, 1.21)	$9.35\text{x}10^{-08}$	$2.10\text{x}10^{-07}$
23.86	5.75 (5.46, 6.03)	6.71 (6.42, 7.0)	0.96 (0.59, 1.33)	$4.13\text{x}10^{-07}$	$7.43\text{x}10^{-07}$

Table 8.3: Comparisons across ages between trajectories that were +/- 1 SD Above for the PRS (N=6,305). PRS: Polygenic Risk Score. DS: Depressive Symptoms. FDR: False Discovery Rate. Upper and lower 95% confidence intervals for the estimates are given in (parenthesis). The low PRS was for trajectories which were 1 SD below. The high PRS was for trajectories which were 1 SD above. Differences were calculated using the delta method. Analysis were adjusted for sex and the first ten principal components of ancestry.



(a) Cross-sectional analysis between the depressive symptoms PRS and depressive symptoms across adolescence. Analysis were adjusted for sex, age and the first ten principal components of ancestry.



(b) Association between depressive symptoms PRS and trajectories of depressive symptoms. Averaged population trajectories of depressive symptoms for greater and less genetic liability (+/- 1 SD PRS). Analysis were adjusted for sex and the first ten principal components of ancestry.

Figure 8.1: Association between depressive symptoms and depressive symptoms across adolescence. PRS: Polygenic Risk Score (with a threshold of 0.005). SMFQ: Short Mood and Feelings Questionnaire (depressive symptoms).

8.6 Discussion

In this analysis, I focused on a cross-sectional analysis and a growth curve modelling approach that utilised a repeated measures framework. In the cross-sectional analysis, I found that greater genetic liability to depression (as measured by a polygenic risk score for depressive symptoms) was associated with higher levels of depressive symptoms throughout adolescence and early adulthood. There were stronger associations between the PRS and depressive symptoms at older ages, with some evidence this varied by the threshold of the PRS at each occasion. The PRS with a threshold of 0.005 generally had the strongest associations across occasions. In the growth curve analysis, I found that a higher PRS for depressive symptoms was associated with higher trajectories of depressive symptoms (i.e., a higher depressive symptoms across development), and that a higher PRS was associated with changes in depressive symptoms over time, as characterised by the linear age term.

These results suggest that a higher PRS is associated with greater child and adolescent depressive symptoms and may influence how depressive symptoms change across an important stage of development. Importantly, we see that those with a higher PRS for depressive symptoms begin to have higher symptoms scores between the ages of 12 and 14. These results suggest that genetic liability may play a role in the onset of adolescent depression. Such results place further emphasis on the idea that depression is not only heritable, but genetic liability may result in non-stable patterns of depressive mood.

These results support previous research on genetic influences for depression as studied in twins [28, 200], and are broadly consistent with previous work examining the association between PRS' and depression in children and adolescents who identified 0.4% explained by the PRS [205]. These results show similar associations with regards to the amount of variance explained by the PRS (between 0.04% to 1.08% depending on age), but I also demonstrated greater variance explained at later ages of development that are consistent with some adult GWAS studies of depression, 1% [9, 156]. This is not surprising as these later ages would be closer to the populations in the original GWAS, but important to highlight as the amount of variance explained by the PRS during adolescence (up to age 18), was never more than 0.63%. Future GWAS that focus on periods such as adolescence will provide the most effective avenue for examining the genetic risk in younger populations.

The repeated measures analysis further supplemented the initial cross-sectional research by highlighting that the PRS had stronger associations as age increased and that differences in trajectories that could be the result of varying genetic liability across development. This supports previous twin research showing larger genetic

effects in later adolescence and young adulthood rather than in early childhood [146, 201]. There are several possible explanations as to why genetic liability may influence change over time. Firstly, genetic liability to depression may act upon biological and hormonal pathways, especially during adolescence [212]. This may result in changes to brain development and hormonal responses that put an individual at greater risk of depression [213]. Secondly, a related explanation for the association between genetic liability and adolescent depression may also be underpinned by a complex genetic and environmental interplay, where genetic liability may manifest differentially over time through gene-environment correlations [151]. Genetic liability to depression may produce evocative effects for some social and behavioural traits, which are then associated with greater depression (i.e., genetic liability may result in individual being more susceptible to stressful life events, which therefore results in greater depression). Thirdly, there is also evidence of interaction effects with later life events, where older individuals with greater genetic risk for depression have higher trajectories of depressive symptoms following the death of a spouse [164]. Fourthly, differences in genetic liability could be the result of measurement error and noise at the varying occasions [120] and it may also be possible for sampling differences to affect the precision of these results.

Previous research has shown that genetic liability (in the form of a PRS) can be included into longitudinal models that examine change in a trait over time [206–208]. Research has suggested that it is also possible to examine genetic influences on age related changes in depression [120]. I was able to expand upon this previous work to examine genetic contributions to varying trajectories of depressive symptoms. I demonstrated that genetic influences may be age specific (i.e., may begin to onset at different times). These results show the benefits of using a repeat measures framework (such as a growth curve model) to quantify the extent to which genetics may influence traits over time. By using the correlation between the repeated measurements, it may be possible to reduce measurement error and boost statistical power, which is why the repeated measures model was able to detect stronger estimates throughout development, compared to the cross-sectional analysis. To ensure that any potential gains from the repeated measures framework were not random, I conducted a negative control analysis examining the association between a PRS of height and trajectories of depressive symptoms, and then a depressive symptoms PRS for trajectories of height. Both showed no evidence of an association suggesting this method could be useful for examining genetic influences for change in psychiatric traits (see appendix 8).

The analysis in this chapter had several strengths. Firstly, I was able to use a large longitudinal population cohort with rich phenotype and genotype data. Few

studies have as many repeated assessments of depressive symptoms, especially across adolescence. I was able to utilise these assessments to accurately characterise trajectories of depressive symptoms. Secondly, I was then able to expand upon previous research by using a repeat measures model that is more powerful than cross-sectional analysis. Some of the benefits of this approach include a boost in power and reduction of measurement error, but I was also able to use the same sample across this analysis as the repeated measures model used full information maximum likelihood (FIML) to account for missing data, which is an advantage over the cross-sectional analysis. Thirdly, I was also able to estimate quantify how depressive symptoms changed over time, which is an extension over the cross-sectional methodology. Using trajectories to estimate change over time in genetics analysis could also be expanded for causal analysis such as time varying mendelian randomization [154], where it may be possible to examine if genetic effects at a particular time are causal for other traits.

However, this analysis also had several limitations. Firstly, this analysis did suffer from attrition as sample sizes varied across ages in the cross-sectional analysis, which may bias the results if missingness is not random. However, one of the advantages of using the repeat measures model is that we can instead use FIML to account for missing data. This approach also minimises the bias that may be present if each occasion (age wave) represents a different sample. However, even this approach may be biased if the data are missing not at random, for example, genetic risk for depression may predict missing assessments [157]. Secondly, depression is a heterogeneous condition and there may be a genetic difference between sum scores, and specific symptoms of depression [214]. Depression symptoms may also differ at different ages [215]. That is to say that the symptoms of depression may differ at younger ages, compared to later ages . I used the same summary score of depressive symptoms throughout this analysis, which therefore only captures the sum of depressive symptoms and does not highlight if certain symptoms of depression (i.e., anhedonia, lack of appetite or depressive thoughts) are more related to genetic liability. Future research should look to examine if different profiles of depression change across time and if these profiles are more related to genetic or environmental factors. Finally, these results lack generalisability to all populations as the original GWAS was conducted on individuals of European ancestry. However, future research is beginning to capture GWAS of non-European populations [216], and future studies will be able to examine the impact of genetic liability on adolescent depression in other populations.

8.7 Conclusions

In conclusion, I found evidence that a depressive symptoms PRS is associated with depressive symptoms across adolescence and young adulthood. This PRS was also associated with how depressive symptoms change over time, providing evidence that higher genetic liability to depression is associated with higher trajectories of depressive symptoms (higher intercept and slope). Growth curve models that use a repeated measures framework may be a useful tool in genetic analysis, providing greater statistical power/measurement precision and the opportunity to examine changes and variation in depression over time. These results add to the body of evidence that genetics may be one pathway involved in the onset and maintenance of adolescent depression.

8.8 Chapter summary

This chapter has shown that greater genetic risk for depressive symptoms (as measured by a polygenic risk score) is associated with higher trajectories of depressive symptoms and has advanced the findings from chapter 5 (that greater polygenic risk is associated with the two more severe trajectories). In doing so, this chapter has primarily addressed the second research objective by showing that polygenic risk plays a role in higher trajectories of depressive symptoms. However, this chapter has also addressed the third research objective by showing that adolescence may be a critical period where genetic risk may begin to manifest, and that young adulthood is where these genetic differences in depressive symptoms are greatest. This chapter has also addressed the fourth research objective by translating the complex quartic polynomial estimates into simpler results that can be easily interpreted and used to highlight genetic differences in depressive symptoms at various ages. This chapter has been the culmination of chapters 4, 5, 6 and 7. In the conclusions chapter, I discuss some overarching themes among these chapters that include comparisons between studies and several limitations

Chapter 9

Conclusions

9.1 Overview

Depression is global mental health disorder that will commonly onset during adolescence, and is associated with cognitive, social and behavioural impairments (Thapar et al., 2012). Depressive mood throughout adolescence can be measured by creating trajectories of depressive symptoms, which can further shed light on the nature and characteristics of depressive mood across stages of development. Previous research has also looked to identify the predictors of less favourable trajectories of depressive symptoms to reduce depressive symptoms and later impairments. However, whilst there is a large body of research that has examined trajectories of depressive symptoms across adolescence, and their antecedents, there are several flaws in much of the previous research. These flaws relate to 1) how long depressive symptoms were assessed for and whether they spanned a long enough duration across developmental periods (i.e., childhood to adolescence, across adolescence and post adolescence), 2) smaller sample sizes in longitudinal studies which can make it difficult to make population inferences and result in biased models (e.g., the creation of small trajectory groups), 3) the (un)availability and use of key risk factors in previous (such as genetic predictors) and 4) interpretation of complex estimates from the trajectory models. This thesis has aimed to address these limitations by answering the four key research objectives:

RQ1. What are the varying patterns of longitudinal depressive symptoms across adolescence?

RQ2. How are genetic and environmental risk factors differentially associated with varying trajectories of depressive symptoms?

RQ3. Are there critical points in trajectories of depressive symptoms which tell us

more about how and when depression changes across adolescence?

RQ4. Can the results from trajectory models be simplified to aid in the interpretation and translation of findings?

In this conclusions chapter, I briefly summarise the research chapters undertaken in this thesis, how they addressed the research objectives and their contribution to the literature. I then consider how these chapters are linked through a series of "local" considerations. Then I examine how this thesis fits within the context of the existing literature by making several "global" considerations. Finally, I highlight some limitations of this thesis and give some thoughts about future work.

9.2 Contributions to the literature

9.2.1 Identifying trajectories of depressive symptoms across adolescence

The aim of chapter 4 was to address the first research objective: "what are the varying longitudinal patterns of depressive symptoms across adolescence?". To answer this, I ran a series of analyses that estimated trajectories of depressive symptoms using two methodologies: 1) the multilevel growth curve approach to estimate population-averaged trajectories and 2) the growth mixture modelling approach to estimate multiple trajectories within the population. This chapter identified several key findings, but also acted as a platform for the rest of the thesis:

1) A quartic polynomial growth curve model best fitted the ALSPAC data when considering a population-averaged approach. Within this analysis, I revealed that population averaged trajectories of depressive symptoms tend to rise until the age of 18, where they then begin to decrease. However, from the age of 22, depressive symptoms then begin to increase again through the age of 24. These trajectories were then used to explore the association between various risk factors and trajectories of depressive symptoms in chapters 6, 7 and 8.

2) Growth mixture modelling analysis suggested that a five-class trajectory solution best fitted the data in ALSPAC when using a multiple-trajectories approach. This resulted in five qualitatively distinct trajectories: those who had consistently low levels of depressive symptoms - stable low, individuals with initially low depressive symptoms but rose throughout adolescence and young adulthood – early-adult onset, individuals who only experienced elevated levels of depressive symptoms during adolescence – adolescent limited, individuals with initially elevated levels of depressive symptoms in childhood which decreased over time – childhood-limited and

individuals with moderate levels of depressive symptoms that continued to rise and stay high– childhood persistent. The trajectories identified here were then used to explore the association between risk factors and trajectories of depressive symptoms in chapter 5.

9.2.2 Genetic and environmental risk factors associated with trajectories of depressive symptoms from adolescence to young adulthood

The main aim of chapter 5 was to address the second research objective: "how are genetic and environmental risk factors differentially associated with varying trajectories of depressive symptoms?". To answer this, I used the five trajectories identified in chapter 4 (via the multiple trajectories approach), and then explored associations between these trajectories with several previously identified and novel risk factors (such as polygenic risk, maternal depression, sex and childhood bullying). As stated in the literature review, this approach is common for exploring the impact of risk factors on trajectories of depressive symptoms due to the ease of running multivariate analysis. Therefore, this chapter was undertaken to provide a holistic analysis for the overarching theme of this thesis (genetic and environmental risk factors for trajectories of depressive symptoms). This chapter drew many comparisons with previous research, but extended the literature with these key findings:

1) Genetic liability to depressive symptoms (as measured via a polygenic risk score) and maternal depression were both associated with the childhood persistent and early adult onset trajectories – the two most severe trajectories.

2) Specific "environmental" risk factors, namely bullying were also associated with these two severe trajectories, but also strongly associated with the childhood limited trajectory (with this trajectory not showing any evidence of an association with genetic liability).

3) Different risk factors have differential effects on the nature of the trajectories of depressive symptoms. However, the fact that risk factors (like bullying) were associated with multiple-subpopulation trajectories is consistent with the notion that more severe trajectories may depend on other prior susceptibilities such as genetic or familial risk.

9.2.3 Sex differences and trajectories of depressive symptoms from childhood to young adulthood: the role of critical points

The aim of chapter 6 was to also address the second research objective and focus on a the role of sex as a risk factor in greater detail. This chapter expanded upon chapter 5 (which showed strong associations between sex and higher trajectories of depressive symptoms) and the existing literature by also addressing the third and fourth research objectives: "are there critical periods in depressive symptoms?" and "can trajectory results be simplified to aid in interpretation and translation?" respectively. To answer these objectives, I used the population averaged trajectories identified in chapter 4 to explore sex differences in trajectories of depressive symptoms and built upon previous research by expanding upon the notion of critical points along these trajectories. This chapter advanced the previous two chapters with the following key findings:

1) Females were more likely to have higher trajectories of depressive symptoms compared to males, and this began to manifest around the age of 12 and continued throughout adolescence and young adulthood.

2) Females also had an earlier age of peak velocity of depressive symptoms (the age where depressive symptoms are getting worse at the fastest rate), with the female age of peak velocity being around 13.5 years old, whilst for males it was much later at around 16 years of age. This seems to coincide with the timing of puberty in both females and males and may identify a period which could be targeted with interventions and preventions.

3) The age at which depressive symptoms were highest was slightly earlier for females (19 years old), although there was little evidence for a difference between females and males (20 years old).

9.2.4 Early childhood trauma and trajectories of depressive symptoms

The aim of chapter 7 was to again address the second research objective, but within the context of childhood trauma as an environmental risk factor. Chapter 5 identified that bullying was a risk factor for higher trajectories, so in this chapter I looked at an extension of bullying: childhood trauma and the number of types of childhood traumas (which can be thought of as an accumulation of different types of traumas - including bullying). This chapter also addressed the third and fourth

research objectives. To address these research objectives, I explored the association between childhood trauma and later population-averaged trajectories of depressive symptoms. I also wanted to examine if the number of childhood traumas might be differentially associated with higher trajectories, and to explore if the results from these models could be translated into an alternative set of parameters that were easier to interpret. This chapter added the following key findings to the literature:

1) Exposure to childhood trauma was associated with higher trajectories of depressive symptoms across adolescence and young adulthood, with the greatest difference in depressive symptoms occurring around the age of 20.

2) Exposure to three or more types of childhood trauma were strongly associated with higher trajectories of depressive symptoms compared to those with none, one or two childhood traumas. Those exposed to three or more types of traumas had trajectories that did not only have a higher starting point at age 10, but also got worse at a much faster rate. The greatest difference in depressive symptoms for those with three or more traumas was observed around the age of 18.

3) Complex model estimates may be more easily interpreted by calculating the predicted difference in depressive symptoms scores at various ages rather than by interpreting the estimated parameters of the depressive symptoms polynomial trajectories directly. This may aid in the interpretation of results and help translate findings from research into practise and policy as specific ages are given to determine when a risk factor may be having the greatest effect.

9.2.5 Association between polygenic risk and trajectories of depressive symptoms

The aim of this final research chapter was to again address the second, third and fourth research objectives, but this time within the context of examining genetic risk for the population averaged trajectories of depressive symptoms. Chapter 5 showed that polyegnic risk may play a role in the onset and maintenance of greater adolescent depressive symptoms and so this chapter looked to expand upon those results using a different approach: the the population-averaged approach. This chapter was therefore the culmination of the previous chapters and sought to expand upon these chapters with the following key contributions to the literature:

1) Genetic risk for depressive symptoms (as assessed by a polygenic risk score) was associated with higher trajectories of depressive symptoms, that seemed to manifest in early adolescence. Greater genetic risk was associated with a higher starting point and a greater rate of change across adolescence.

2) Both cross-sectional and growth-curve models revealed that genetic risk for depressive symptoms had a stronger effect in young adulthood, compared to adolescence and late childhood. However, results were more precise in the growth curve framework suggesting repeated measures analysis may be a useful tool in genetic analyses compared to traditional cross-sectional methods.

3) Results from the growth curve model may be more easily interpreted when comparing depressive symptoms scores at varying ages (i.e., comparing depressive symptoms scores for high vs low risk at age 12, 14 or 16 etc. . .), and this framework could be useful for examining characteristics of depressive symptoms such as the age of onset or age of greatest difference.

9.3 Local considerations

In the following two sections I give some "local" considerations that are specific to this thesis (and how the research chapters are linked) and then highlight some "global" considerations that are applicable to this thesis, but also to the growth curve research literature in general.

This thesis has used a large population study to examine the genetic and environmental contributions to trajectories of depressive symptoms. I first looked to identify trajectories of depressive symptoms using two varying methods (the population-averaged and multiple-subpopulation approach). I then took these trajectories and explored if different genetic and environmental risk factors would provide differential associations. Finally, I then explored if the results from these studies could be expanded (via the notion of critical points) and simplified to help aid in interpretation and translation into practise and policy. As a result, this thesis has addressed several limitations identified from previous research and answered four research objectives that have contributed to the literature of trajectories of depressive symptoms. Still, there are several "local" issues that are common across research chapters in this this thesis.

9.3.1 Comparing methodological approaches

The first issue worth discussing is whether it is appropriate to compare results between population-averaged trajectories (multilevel growth-curve models) and multiple trajectories (growth mixture modelling). The literature review in chapter 2 highlighted that each approach has strengths and weaknesses, and that each approach could be tailored to address specific research questions and a variety of data.

For example, if the research question was to examine what risk factors are associated with trajectories that are characteristic of early adult onset depressive symptoms, then the multiple trajectories approach may be more appropriate. If the research question was to explore the average population trajectory between two groups (i.e., females vs males), then the population averaged approach may be more appropriate. Previous research has suggested that the choice in method depends on whether the researcher believes trajectories should be classified by discrete or continuous heterogeneity, so ultimately the two approaches have a different focus on emphasis so it not as simple to state that one approach is better than the other. The results from this thesis suggest that both methods can complement, not just oppose one another. As mentioned in the literature review, it is challenging to compare one population averaged trajectory compared to five multiple distinct trajectories (like in chapter 4), but if certain risk factors are being similarly associated between the two methods, then this suggests that both approaches can be used for similar research questions and that it may be advisable to utilise both approaches within the same study to untangle the complex aetiology of depressive symptoms. For example, female sex was associated with all the "higher" trajectories in the multiple trajectories approach but was also associated with a much higher/steeper trajectory of depressive symptoms in the population averaged approach. Likewise, genetic risk was associated with the childhood persistent and early-adult onset trajectories in the multiple trajectories approach and associated with a higher trajectory in the population averaged approach. With the latter approach, the greatest difference between higher and lower risk was observed in young adulthood, also where both the childhood persistent and early-adult onset trajectories end up. Such analysis indicates that both approaches can give similar interpretations and inferences in some instances. However, it is important to state that distinguishing between discrete or continuous heterogeneity could also lead to contrasting estimates (and then inferences), and this is likely why no research has used both approaches within the same study. However, as stated above, the choice in method used will vary much depend on the overarching research question and so in many studies it may not be suitable to use both approaches.

9.3.2 Varying effect sizes

A second consideration relates to the effect sizes of the varying genetic and environmental risk factors. When comparing across the chapters, a common theme emerges in that some risk factors are more strongly associated with trajectories of depressive symptoms than others. This can be demonstrated by highlighting the results from the population averaged trajectories approach as female sex had a difference of 2.13

short mood and feelings questionnaire (SMFQ) points at age 16, whilst genetic risk to depressive symptoms had a difference of only 0.73 SMFQ points. Previous research has shown that sex differences in depression are large [22], and that directly measured genetic liability to depression (i.e., via a polygenic risk score) is likely to be small/modest [9], so these results are not surprising. Still, these comparisons are interesting to note as they help shed light on what are the most prominent risk factors for greater depressive symptoms across adolescence and when they could be having their greatest effects, which could in turn help develop preventions and interventions that could be risk factor or timing specific.

9.3.3 Benefited interpretation and translation

Thirdly, one of the key limitations in previous research has been the inability to translate complex model estimates (e.g., sex specific estimates of flexible polynomial trajectories) into more interpretable findings. The results from chapter 5 regarding the association between various genetic and environmental risk factors and the multiple trajectories (e.g., stable low) was easy to interpret and could be translated into policy and practise if needed. However, the results from the population-averaged trajectories are more complex, especially when considering the underlying growth parameters (linear, quadratic, cubic and quartic age functions) in isolation as researchers often attempt to do. The overall graphical representation of the population averaged trajectory is easy to understand yet comparing lines on a graph is should not be the only method that guides policy and practise. Growth curve models offer much more than graphical representations and can be used to quantify the nature and changes of depressive symptoms in great detail that go beyond examining figures. The estimates from these growth-curve models can be used to inform exactly when symptoms are beginning to rise or the score at a particular age and how the score for one trajectory contrasts with other trajectories. However, as stated in chapter 7, it is hard to interpret a set of estimates which are in opposing directions (i.e., positive linear and quadratic effects, but negative cubic and quartic effects, for example). This thesis has attempted to address this limitation by providing an "alternative parameterisation" framework which aims to make the model estimates simpler to interpret and calculates the difference in depressive symptoms scores at various ages. This approach is likely to be useful when growth curves move beyond simple quadratic models and require more advanced modelling. These simplified results may help aid in the interpretation of complex results (as they are categorised into groups) and may join the multiple trajectories approach in being easier to understand by individuals without statistical backgrounds. Likewise, by identifying multiple time points where there could be differences in population-averaged tra-

jectories (i.e., between females and males, low vs high genetic risk, or number of traumas), it is possible identify when risk factors are likely to exert the greatest effects – or in other words, when is a risk factor having the worst effect on depressive symptoms? This "alternative parameterisation" framework builds upon previous research as it now possible to visually see the differences (via figures), as well as quantify the estimates underlying the figures and statistically compare them at different stages of development (i.e., at age 12 compared to age 24).

9.4 Global considerations

9.4.1 Viable data?

There are also several global considerations that should be made regarding how this thesis fits in with the existing literature on genetic and environmental contributions to trajectories of depressive symptoms. Firstly, as highlighted in the literature review, many studies do not have truly longitudinal data that covers multiple developmental periods (i.e., childhood to adolescence, across adolescence and post adolescence). As depression will commonly onset during adolescence [3, 16], it is important to have data that examines mood prior, during and after this period in order to fully maximise our ability to adequately track changes in depressive symptoms. This thesis has maximised the use of a well detailed longitudinal cohort, with nine repeated assessments of depressive symptoms across these stages of development. In addition, ALSPAC is considered to be a largely representative cohort, and so the nature of these trajectories is likely to extend across other populations. Other longitudinal studies have shown similar characteristics of depressive symptoms trajectories with similar waves of data [99, 101, 102]. Furthermore, other research has found similar results when examining the association between risk factors and trajectories of depressive symptoms [34, 43].

9.4.2 Repeated measures benefits

A second consideration is whether there are additional benefits of using a repeated measures framework compared to a simpler model that only uses one occasion like in several studies [205, 217]. As stated in the introduction, there are obvious advantages to using the repeated measures model such as the ability to examine depressive symptoms across a period of development (i.e., before, during and after adolescence), which therefore provides more information about the nature of depressive symptoms. However, this thesis has also provided further evidence that a repeated measures

framework that derives trajectories of depressive symptoms can: 1) help identify critical periods in depressive symptoms, that might be targetable for prevention and intervention; 2) determine when risk factors might be having their greatest effect and comparing this across multiple stages of development and; 3) potentially boost statistical power and reduce measurement error that can make for a more precise associations compared to simpler cross sectional methods.

9.4.3 Public health and policy implications for growth-curve research

A third and final consideration is whether the findings from growth-curve models of depressive symptoms have any public health or policy implications, alongside research into the aetiology of adolescent depressive symptoms. Estimating a trajectory of depressive symptoms is useful for examining when symptoms are getting worse, when they are highest and when they are potentially getting better. As demonstrated in this thesis, it is also possible to examine what risk factors play a role in how depressive symptoms develop and change over time (e.g., sex differences or childhood trauma). From a public health or policy standpoint, understanding the nature of these trajectories (i.e., when they onset, the severity and chronicity) could be useful for identifying when a treatment or intervention could be implemented (if it could be implemented at all) or to help services or schools be aware of the patterns so that worsening mood may be identified quicker. Likewise, identifying critical points could be of great use (especially in chapter 6 with the notion of the age of peak velocity) as this could potentially be utilised to prevent depressive symptoms from rising in the first instance (which has beneficial downstream consequences such as increased social functioning or educational attainment). Additionally, as shown in chapters 7 and 8, critical points can also inform when a risk factor is having the greatest effect on depressive symptoms, which could aid in the timing of treatments. The identification of critical points could be achieved through simpler cross-sectional models, yet these repeated measures models are more powerful and precise than cross-sectional methods (which have conceptual and statistical flaws, e.g., only one time point; increased measurement error at one occasion). Both the population-averaged and multiple-subpopulations approach build upon the cross-sectional approach and there appears to be the potential for growth curve research to be used to help inform public health and policy makers, if the information is correctly presented and translated.

9.5 Limitations

As with most research, there are several limitations that should be addressed within this thesis. Whilst, I have discussed specific limitations of the research in each chapter, there are several 'broader' limitations that are common among these chapters. I now provide an overview of these broader limitations and how they could impact on the thesis.

The first limitation is that this thesis exclusively used data from ALSPAC and in particular, ALSPAC data on the children/young people and so the results presented here may not be generalisable to other cohorts and populations. ALPSAC is considered to be representative of the population but may suffer from bias (as discussed later). Reassuringly, the pattern of depressive symptoms observed in this thesis matched other studies, as identified in the literature review - suggesting these results (in particular the association between risk factors and trajectories of depressive symptoms) may be applicable to other populations. The results identified here could be replicated in other cohorts such as the Add Health or E-Risk cohorts, if the data were permitted. However, the fact that I was unable to compare these specific analyses in other cohorts is a limitation of this thesis.

Cohort attrition is a limitation in any longitudinal study, and ALSPAC is no different. As shown in the data and methods chapter, the sample size for completion of the SMFQ tended to decrease throughout the study – from a sample size of over 7000 individuals around age 10 to just over 3000 in age 24. One way to address missing data in longitudinal growth curve studies is to use full information maximum likelihood (FIML) to take account of the missing data [138, 139]. This means that once we account for the depressive symptoms scores which we do observe, the probability a score is missing at any occasion does not depend on its unknown level of depressive symptoms at that occasion. The FIML approach assumes that the data are missing at random, however some evidence suggests that depressive symptoms data in ALSPAC should be considered missing not at random. Recent research using genetic risk for psychiatric traits has shown that higher genetic liability of depressive symptoms is associated with less participation in the ALSPAC study [157]. The authors suggested that participation within ALSPAC may not be dependent on other factors, and a lack of participation may not be random, implying that attrition and selected participation may bias cohort studies like ALSPAC. Attrition and selected participation for the depressive symptoms measures may bias results in this thesis but it is not currently possible to examine if the data are or are not missing at random. Likewise, if individuals with greater depressive symptoms are more likely to have missing data, than the estimates presented in this thesis are

more likely to be underestimating the true depressive symptoms scores, rather than overestimating them.

Another limitation of this thesis could result from the choice of modelling used to estimate multilevel growth curves throughout this thesis. Previous research has shown that using higher order polynomials (such as quadratic and cubic growth terms) can be used to model trajectories of depressive symptoms across adolescence [101, 102]. However, this is the first study to use quartic polynomials to capture the complex changes in depressive symptoms. I chose to use a quartic polynomial model as there were four distinct changes in the SMFQ descriptive statistics that resembled a quartic model (see data and methods section). Likewise, when assessing model fit, a quartic polynomial model best fitted the data as assessed by a series of model fit statistics (AIC, BIC, deviance and likelihood ratio tests). The quartic model was also preferred to other polynomial models such as higher order fractional polynomials. However, this does not necessarily mean that the quartic model is the optimal model for estimating complex trajectories of depressive symptoms and as discussed in previous chapters, one limitation of this model is the resulting complex estimates that are derived from model. Other research on childhood height and weight has used linear splines or piecewise models to estimate trajectories of childhood growth [61, 135]. This approach, which essentially estimates a linear trajectory between certain ages (i.e., linear growth between 10 to 12, 12 to 18, 18 to 22, 22 to 24) could also be applied to trajectories of depressive symptoms, especially if future waves of depressive symptoms fluctuate and become harder to model using polynomial models. There is currently no evidence of splines being used to measures trajectories of depressive symptoms, and this may be because critics of the spline approach claim that a series of linear changes do not capture the complexity of childhood growth and unrealistic of the nature of depressive symptoms. That said, other research utilising a structural equation approach has estimated trajectories of depressive symptoms across adolescence, and then separately in young adulthood using a similar model to splines [106]. It may be that estimating specific periods of growth (i.e., childhood to adolescence, across adolescence, adolescence to young adulthood) may be one approach for future research, both in ALSPAC and other longitudinal studies.

A further limitation in this thesis is the issue of time-varying covariates (or risk factors). In several of the research chapters, the risk factors have been time-invariant – they do not change over time (e.g., sex or genetic risk). However, other risk factors such as maternal depression, bullying and childhood trauma are not stationary traits and may change over time [148, 218]. This thesis did not consider time-varying covariates as the focal point of this thesis was to examine genetic and environmental contributions to trajectories of depressive symptoms in the first

instance. Modelling time-varying risk factors such as maternal depression or bullying would require an additional trajectory (or crossed-lagged approach) of those risk factors, thus providing further complexity and distraction to this thesis. However, whilst I did not examine the impact of time-varying risk factors, I acknowledge that this thesis suffers from the possibility that time-varying risk factors are likely to play an important and reciprocal role in the nature of trajectories of depressive symptoms. For example, previous research has shown that depressive symptoms and alcohol use across adolescence have a bi-directional relationship that may influence current and later behaviours [5]. It is likely that bi-directional relationships may also occur between depressive symptoms and the risk factors mentioned within this thesis, and future work should look to build upon the research in this thesis by taking into account time-varying risk factors that either use additional trajectories through a bivariate response model or cross-lagged approaches that utilise the development of multiple traits.

On a related note, this thesis may also be subject to residual confounding which may have biased some of these results even after adjusting for relevant confounders. Whilst every attempt was made to to include confounding variables into these chapter (for example in researh chapters 2 and 4, which contain a high degree of environmental data), there is still the possibility that additional important confounding factors were not included. This can be due to the availability of the data within ALSPAC, but also as a result of the models chosen. For example, the multivariate analysis in research chapter 2 included a variety of biological, genetic and environmental data and thus it is possible that some confounding varibales that were included in the model may also be mediators or indeed on the causal pathway. The literature regarding residual confounding when considering both genetic and environmental variables has yet to be fully established, and so this opens up a potential limitation for this thesis.

A final limitation of this thesis relates to the assessment of depressive symptoms within ALSPAC: the SMFQ. The SMFQ has been used in many epidemiological studies around the world [14, 15, 129] and extensively in ALSPAC [13, 75, 87, 108, 219], but there are potential limitations of its use in this thesis. The first is that the SMFQ was only assessed from the ages of 10. Prior to this, alternative measures of mood were used, that cannot be translated between measures. This lack of data before the age of 10 limits the ability to examine the direct effects of early life measures such as maternal depression or childhood anxiety. However, to have data from late childhood and all the way through to young adulthood is a major strength of ALSPAC and this thesis. One potential caveat of this is that research using the SMFQ in adults, and in particular examining the transition to adulthood are

scarce as the SMFQ was originally designed for use in younger individuals [14, 129]. Therefore it is unclear how these results may replicate in older populations or the transitions in other populations. Alternative studies in older popualtions tend to use the Centre for Epidemiological Studies Depression Scale (CES-D), which may be more effective for detecting clinical thresholds of depression [164]. The second limitation is whether it is appropriate to use the SMFQ for growth curve analysis, when the SMFQ only assesses depressive symptoms within the last two weeks and was measured at least a year apart (or in some cases, three years apart). Given how depression is particularly volatile during adolescence, an argument could be made that the SMFQ does not appropriately capture the full nature of depressive symptoms when it is assessed within this framework. An alternative approach could look to maximise linked health records data, although a diagnosis would more likely be used rather than depressive symptoms. Alternatively, more frequent assessments of mood scores could be assessed in schools (e.g., every two weeks) giving a possible wealth of data that could be linked – although this approach would be expensive and time consuming. Given the costs of collecting data and managing a multifactorial study, there is unlikely to be perfect method for assessing depressive symptoms and the current methodology is probably more than adequate for this thesis.

9.6 Future research

This thesis has addressed several limitations of previous work and contributed to the ongoing literature on trajectories of depressive symptoms. However, there are still many unanswered questions and more research that follows directly on from the work presented in this thesis.

Firstly, whilst the use of depressive symptoms summary scores has been useful for determining the overall nature of depressive symptoms across development, there is a growing consensus that summary scores of depressive symptoms may not be adequate to fully capture the heterogeneity of depressive mood [220]. Depression is a complex disorder that is characterised by several specific symptoms such as anhedonia, changes in appetite, thoughts of suicide and fatigue [3]. Individuals with depression may experience some, or all these symptoms, but identifying which symptoms to treat is vital for intervention [87]. Summary scores of depressive symptoms do not discriminate between these symptoms, and so it is difficult to determine what symptoms may need to be treated and if some symptoms are more prevalent at different stages of development. Previous research has shown that symptoms do differ between adolescence and adulthood [87], but importantly, previous research has also shown that some risk factors may differentially predict specific symptoms of

depression [221]. Given how heterogeneous depressive symptoms are, future research should consider approaches that examine trajectories of specific symptoms (in this case items of the SMFQ) and risk factors for these trajectories as this could help target specific forms of treatment and interventions and identify if certain symptoms (or items) are more prevalent at specific times.

Secondly, whilst this thesis has examined the genetic and environmental contributions to trajectories of depressive symptoms, the next logical step would be to consider the impact of these trajectories on later distal outcomes. Previous research has shown that the multiple trajectories approach can derive depressive symptoms that are good predictors of later distal outcomes such as social and cognitive functioning, educational attainment and psychopathology [32, 43]. However, in these studies the sample sizes remain small to modest and these trajectories do not have a long duration of follow up. The trajectories identified within this thesis could further examine the relationship between depressive symptoms across adolescence and later outcomes. In fact, one very recent study has used the multiple trajectories approach within ALSPAC and found that the two more severe trajectories (the childhood persistent and early-adult onset trajectories) were strongly associated with a not in education, employment or training (NEET) status [130]. Further work using these trajectories should also explore other outcomes such as psychopathology in adulthood and other forms of social and cognitive functioning. Trajectories could also be associated with later outcomes using the population averaged approach as in previous research [108]. This work could also be expanded to have models that jointly consider risk factors and later outcomes within the same model with trajectories as potential mediators. Such work could be vital for exploring how a risk factor manifests itself in later life and future research could examine the impact of this manifestation, when trajectories are lower or higher. This may provide clinicians and policy makers with a tool that demonstrates that if depressive symptoms can be lowered across adolescence (the mediator), then the impact between a risk factor and a later outcome may also be lowered. Future research should explore these kinds of models with the aim of showing that trajectories of depressive symptoms could be modified and reduced.

9.7 Concluding remarks

Trajectories of depressive symptoms have a complex and multifactorial aetiology, that is comprised of both genetic and environmental contributions. This thesis looked to examine these contributions through a series of research objectives. Specifically, this thesis identified two forms of trajectories: population averaged trajecto-

ries and multiple trajectories. There appeared to be some specificity in that certain risk factors were more strongly associated with trajectories of depressive symptoms such as female sex, genetic risk for depressive symptoms, bullying and childhood trauma. These results appeared to be common across the varying methodologies, giving weight to the idea that different modelling approaches can support one another. This thesis also looked to expand upon previous work by estimating critical points in trajectories of depressive symptoms and providing an alternative way of displaying estimates from complex models that could be more easily interpreted. This thesis has contributed several key findings to the existing literature and helped further knowledge regarding the nature of trajectories of depressive symptoms. However, this thesis is not without its limitations that should be fully considered and future work could expand upon this work to further untangle the complex aetiology of depressive symptoms.

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Appendix A

Appendix

Appendix 2: A Review on The Nature of Trajectories of Depressive Symptoms from Childhood to Young Adulthood: Methods, Predictors and Future Considerations

Appendix 4: Identifying Trajectories of Depressive Symptoms Across Adolescence and Young Adulthood

Appendix 5: Genetic and Environmental Risk Factors Associated with Trajectories of Depressive Symptoms from Adolescence to Young Adulthood

Appendix 6: Sex Differences and Trajectories of Depressive Symptoms from Childhood to Young Adulthood: The Role of Critical Points

Appendix 7: Childhood Trauma and Trajectories of Depressive Symptoms Across Adolescence

Appendix 8: Association Between Genetic Liability and Trajectories of Depressive Symptoms

Appendix 2 – A Review on The Nature of Trajectories of Depressive Symptoms from Childhood to Young Adulthood: Methods, Predictors and Future Considerations

Appendix Table 2.1

Author	N	Age/Grade Range	Sample	Measure	Method	Years Follow Up	Waves	Trajectories	Main Findings
Brendgen et al. (2005)	414	11-14	Canadian Children	CDI	GMM	3	4	4	Consistently low (47.7%), Consistently moderate (30.3%), Increasing (12.7%), Consistently high (9.3%).
Brendgen et al. (2010)	201	11-13	Canadian Children	CDI	SPGBM	2	3	3	Low stable (75%), Increasing (15%), High stable (10%).
Briere et al. (2015)	6910	12-16	Canadian Children	CES-D	GMM	4	5	5	Stable-low (68.1%), Increasing (12.1%), Decreasing (8.7%), Transient (8.7%), Stable-high (2.4%).
Brook et al. (2014)	607	14-32	American Adolescents	5 DS Items	GMM (Joint)	22	6	5	5 joint trajectories. One group had high depressive symptoms and high smoking. Another group had low depressive symptoms and low smoking.
Chaiton et al. (2013)	1293	12-16	NDIT	6 DS Items	SPGBM	5	20	3	High (Males: 14% & Females: 28%), Moderate (Males:

									36% & Females: 43%), Low (Males: 50% & Females: 29%).
Colman et al. (2007)	4627	13-53	1946 British Cohort	Rutter B2	LCA	40	5	6	Absence of symptoms (44.8%), Adult-onset moderate symptoms (11.3%), Repeated moderate symptoms (33.6%), Adolescent symptoms with good adult outcome (5.8%), Adult-onset severe symptoms (2.9%), Repeated severe symptoms (1.7%).
Costello et al. (2008)	11,559	11-18	ADD Health	CES-D	SPGBM	7	3	4	No depressed mood (28.7%), Low depressed mood (59.4%), Early high depressed mood (9.5%), Late escalating depressed mood (2.4%).
Cumsille et al. (2015)	1072	14-17	Chilean Adolescents	CES-D	GMM	3	4	4	High persistent (12.3%), Low stable (55.8%), Low increasing (17.0%), High decreasing (14.9%).

Dekker et al. (2007)	2076	4-18	Dutch Community Sample	CBC	SPGBM	14	5	12	Males: Very low decreasing (39.6%), Low stable (39.8%), Moderate increasing (14.7%), High decreasing (2.3%), High childhood peak (1.6%), Increasing high (1.9%). Females: Low decreasing (19.1%), Very low increasing (13.9%), Low stable (53.5%), Moderate stable (10.8%), adolescence onset increasing high (1.5%), high increasing (1.2%).
Diamantopoulou et al. (2011)	1423	11-18	ZHLS	YSR	GMM	14	7	6	Males: Low (92%), Decreasing (3%), Increasing (5%). Females: Low (80%), Decreasing (8%), Increasing (12%).
Duchesne and Ratelle (2014)	414	11-16	Canadian Children	CDI	SPGBM	5	6	4	Moderate stable (54.57%), Low stable (27.16 %), Moderate increasing (11.30 %), High declining (6.97 %).

Duivis et al. (2015)	1166	11-16	TRAILS	YSR	LCA	5	3	5	High (6.9%), Moderate (27.2%), Increasing (20.6%), Decreasing (30.2%), Low (15.2%).
Ellis et al. (2017)	243	12-18	ADS	CES-D	LCGA/ GMM	7	4	4	Low stable (65.4%), Moderate early (20.2%), Severe early (3.3%), Late (11.1%).
Fernandez Castelao and Kroner-Herwig (2013)	3902	11-14	German Children	YSR	GMM	4	4	4	Very high-stable (1.1 %), High-decreasing (8.1 %), Moderate-slightly increasing (28.3 %), Low-increasing (62.5 %). Stratified by sex - Males: High-strong decreasing (4.8 %), Moderate-stable (25.6 %), Low-slightly increasing (69.6 %). Females: Very high-stable (1.3 %), High-slightly decreasing (9.7 %), Moderate-slightly increasing (32.7 %), Low-increasing (56.3 %).
Ferro et al. (2015b)	2825	10-24	NLSCY	CES-D	LCGA	14	8	3	Minimal (55%), Subclinical (39%), Clinical (6%).

Fleming et al. (2008)	951	Grades 8-11	RHC	SPQ	MGLGCM	4	4	2	2 trajectories, one for males and one for females and their relation to concurrent substance use
Heath and Camarena (2002)	268	Grades 6-8	American Children	CDI	ANOVA	3	6	6	Low stable (Males: 27%; Females: 27%), Medium stable (Males: 30%; Females: 34%), High stable (Males: 8%; Females: 10%), Episodic (Males: 21%; Females: 9%), Decreaser (Males: 9%; Females: 4%), Increaser (Males: 6%; Females: 16%).
Kingsbury et al. (2016)	9166	10-18	ALSPAC	SMFQ	LCGA	8	6	4	Stable low (61.8%), Stable Moderate (26.8%), Moderate Increasing (6%), Consistently High (5.5%).
Leadbeater et al. (2012)	662	12-18	HYS	BCFPI	MGLGCM	6	4	6	3 trajectories for males and 3 trajectories for females.
Lee et al. (2017)	537	15-26	FTP	SCL-90-R	LT-GMM	11	6	6	Adolescence: High and declining (11%), Moderate and escalating (14.1%),

									Low and stable (74.9%). Young adulthood: High and declining (8.6%), Moderate and escalating (5.3%), Low and stable (86.1%).
Lubke et al. (2016)	15,124; 12,225	7-12; 14-18	YNTR; ANTR	CBC; YSR	GMM	NA	6	> 2	Separate trajectories and classes derived for males and females.
Mazza et al. (2010)	951	Grades 2-8	RHC	SPQ	SPGBM	6	6	5	Low depressed stables (27%), Low depressed risers (22.7%), Mildly depressed stables (27.7%), Moderately depressed changers (11%), Moderately depressed risers (11.6%).
Mezulis et al. (2014)	382	11-18	WSFW	CDI	GMM	7	4	3	Stable low (51%), Increasing (37%), Early high (12%).
Mumford et al. (2013)	8320	15-27	NLSCY	MHI-5	GGMM (Joint)	8	5	5	Stable normal weight, stable good mental health (82.2%), Consistently obese, stable good mental health (6.8%), Overweight

									becoming obese, declining mental health (5.6%), Stable normal weight, improving mental health (3.3%), Morbid obesity, stable good mental health (2.1%).
Olino et al. (2010)	1709	16-30	American Adolescents	K-SADS	LCGA	14	4	6	Persistent depression (1.3%), Persistent anxiety (2.1%), Later onset of anxiety with increasing depression (3.7%), Increasing depression (22.8%), Anxiety with early recovery (5.0%), Without anxiety/depression (65.1%).
Otten et al. (2010)	428	13-20	FHS	GSE	GMM	Not reported	5	3	High (25%), Medium (50%), low (25%).
Reinke et al. (2012)	361	10-16	American Adolescents	CDI	GMM	6	6	4	Increasing symptoms (5.1 %), High levels of depressive symptoms (5.2 %), Decreasing depressive symptoms (8.9 %), Low levels of depressive symptoms (80.9 %).

Repetto et al. (2004)	579	14-17	African-American Adolescents	BSI	ANOVA	4	4	4	Consistently high (15.9%), Consistently low (21.1%), Decreasing (41.8%), Increasing (21.2%).
Rodriguez et al. (2005)	925	Grades 9-12	American Adolescents	CES-D	GGMM	4	4	3	High (23%), Moderate (44%), Low (33%).
Sabiston et al. (2013)	860	12-18	NDIT	6 DS Items	SPGBM	6	21	3	Low and declining (37.8%), Moderate and stable (41.6%), High increasing (20.6%).
Sallinen et al. (2016)	112	13-16	Finish adolescents	MFQ	SPGBM	2	3	4	Minor (63%), Medium (25%), Decreasing symptoms (5.5%), Escalating (6.5%).
Salmela-Aro et al. (2008)	297	18-25	Finish Young Adults	BDI	GMM	10	7	3	Low (23%), Moderate (61%), High/increasing (16%).
Stoolmiller et al. (2005)	206	15-24	Oregon Youth Study	CES-D	GGMM	9	10	4	Very low (6%), Moderate decreasing (34%), High decreasing (36%), High persistent (24%).
Weeks et al. (2014)	6337	4-14	NLSCY	OCHD	LCGA	10	8	5	Low stable (68%), Adolescent onset (10%), Moderate stable (12%), High

									childhood (6%), High stable (4%).
Whalen et al. (2016)	348	4-13	PDS	PAPA; CAPA	GMM	10	8	6	Males: Low (51.88%), Medium (31.25%) and High (16.87%). Females: Low (56%), Medium (35.3%) and High (8.7%).
Wickrama et al. (2009)	14,058	11-18	ADD Health	CES-D	ANOVA; SEM	7	3	4	Consistently-Low (24.5%), Decreasing (46.5%), Increasing (22%), Chronically-High (7%).
Wickrama and Wickrama (2010)	11,500	13-23	ADD Health	CES-D	LCA	10	4	4	Low (63%), Decreasing (8%), Escalating (3%), Chronically moderate-high (13%).
Wiesner and Kim (2006)	985	15-17	MAVS	CES-D	DTA	2	3	7	Males: Rarely depressed (4.5%), Low (31%), Medium (51.2%), High (13.2%); Females: Low (21.3%), Medium (52.6%), High (26%).
Willoughby and Fortner (2015)	4412	Grades 9-12	NLSCY	CES-D	LCGA (Joint)	4	4	8	Males: Low co-occurrence (43.8%), High co-occurrence (10.1%), High dep

									only (14.5%), High alcohol only (31.6%). Females: Low co-occurrence (35.6%), Moderately high co-occurrence (13.8%), High dep only (13.5%), Moderate alcohol only (37%).
Yaroslavsky et al. (2013)	719	14-30	OADP	CES-D	GMM	14	4	3	Low decreasing (24%), Moderate-decreasing (44%), High stable (32%).

Table 2. A summary of group-based trajectory studies examining trajectories of depressive symptoms from childhood to young adulthood. **ANOVA:** Analysis of Variance, **ADD Health:** National Longitudinal Study of Adolescent Health, **ADS:** Orygen Adolescent Development Study**, ALSPAC:** Avon Longitudinal Study of Parents and Children, **BCFPI:** Brief Child and Family Phone Interview, **BDI:** Beck Depression Inventory, **BSI:** Brief Symptom Inventory, **CAPA:** Child and Adolescent Psychiatric Assessment, **CBC:** Child Behavior Checklist, **CDI:** Children's Depression Inventory, **CES-D:** Centre for Epidemiological Depression Scale, **DS:** Depressive Symptoms, **DTA:** Dual Trajectory Analysis, **FHS:** Family and Health Study, **FTP:** Family Transitions Project, **GGMM:** General Growth Mixture Modelling, **GMM:** Growth Mixture Modelling, **GSE:** Global Negative Self-Evaluation Scale, **HYS:** Victoria Healthy Youth Survey, **K-SADS:** Schedule for Affective Disorders and Schizophrenia for School-Age Children, **LCGA:** Latent Class Growth Analysis, **LCA:** Latent Class Analysis, **LT-GMM:** Latent Transition Growth Mixture Model, **MAVS:** Middle Adolescent Vulnerability Study, **MFQ:** Mood and Feelings Questionnaire, **MGLGCM:** Multiple-Group Latent Growth Curve Models, **MHI-5:** Mental Health Inventory 5-Item**, NDIT:** Nicotine Dependence in Teens Study, **NLSCY:** National Longitudinal Survey of Children and Youth, **OADP:** Oregon Adolescent Depression Project, **OCHS:** Ontario Child Health Study, **PAPA:** Preschool Age Psychiatric Assessment, **PDS:** Preschool Depression Study, **RHC:** Raising Healthy Children, **SCL-90-R:** Symptom-Checklist-90-Revised, **SES:** Socio-economic Status, **SPGBM:** Semiparametric Group Based Models, **SPQ:** Seattle Personality Questionnaire, **SMFQ:** Short Mood and Feelings Questionnaire, **TRAILS:** TRacking Adolescents' Individual Lives' Survey, **WSFW:** Wisconsin Study of Families and Work, **YNTR:** Young and Adult Netherlands Twin Register, **YSR:** Anxious/Depressed scale of Youth Self-Report, **ZHLS:** Zuis-Holland Longitudinal Study.

Appendix Table 2.2

Author	N	Age/Grade Range	Sample	Measure	Method	Years Follow Up	Waves	Main Findings
Adkins et al. (2009)	18764	11-18	ADD Health	CES-D	LCM	7	3	4 trajectories for males and 4 for females depending on ethnicity, SES and stressful life events.
Adkins et al. (2012)	1909	11-18	ADD Health	CES-D	Mixed-effects models	7	3	4 trajectories for males and 4 for females depending on CES-D score.
Brown et al. (2007)	20126	11-18	ADD Health	CES-D	LTA	7	3	4 trajectories for males and 4 for females depending on ethnicity.
Chen et al. (2011)	12330	11-18	ADD Health	CES-D	LCM	7	3	4 trajectories under 15 years old & 4 trajectories over 15 years old (Chinese-American males, Chinese-American females, White-American males, White-American females).
Edwards et al. (2014)	6182	12-17	ALSPAC	SMFQ	LGM	5	4	1 trajectory for males and 1 for females.
Ferro et al. (2015a)	2825	10-24	NLSCY	CES-D	MLM	14	8	2 trajectories, one for chronic illness and one for healthy.
Galambos et al. (2006)	920	18-25	Canadian Adolescents	CES-D	MLM	7	5	2 overall trajectories, one for males and one females. 3 for conflict with parents.
Garber et al. (2002)	240	Grades 6-11	American Adolescents	CDI	LFGM	6	6	4 trajectories identified for different attributional styles.
Gaysina et al. (2011)	4559	15-53	1946 British Cohort	Rutter B2	MLM (Joint)	38	6	8 trajectories: 4 each for males and females: adolescent-onset repeated, adolescent-onset with good adult outcome, adult-onset repeated.

Ge et al. (1994)	376	9-20	IYFP	SCL-90-R	LGM	4	4	1 trajectory for males and 1 for females.
Ge et al. (2001)	451	Grades 7-12	IYFP	SCL-90-R	MLM	6	5	1 trajectory for males and 1 for females. 3 trajectories for pubertal status. 3 trajectories for pubertal transition.
Ge et al. (2006)	550	12-23	FTP	SCL-90-R	MLM	10	11	4 trajectories: 2 each for males and females from divorced and non-divorced families.
Guo and Tillman (2009)	2286	11-18	ADD Health	CES-D	MLM	7	3	2 trajectories for DRD2 and DRD4 genetic variants.
Hankin (2009)	350	11-17	American Adolescents	CDI	MLM	5	4	1 trajectory for males and 1 for females.
Kennedy et al. (2010)	100	Not Reported	American Children	CDI	MLM	2	6	4 trajectories for males and females with high/low support.
Kouros and Garber (2014)	240	Grades 6-12	American Children	CDRS-R	MLM	6	7	1 population trajectory established.
Mahedy et al. (2017)	5539	13-18	ALSPAC	SMFQ	LGM	5	4	2 high and low trajectories for both males and females.
Marmorstein (2009)	20728	11-18	ADD Health	CES-D	MLM	7	3	4 trajectories identified in relation to alcohol problems.
Marshal et al. (2013)	12379	14-27	ADD Health	CES-D	LCM	13	4	4 trajectories identified regarding sexuality.
Meadows et al. (2006)	18924	11-18	ADD Health	CES-D	LTA	7	3	1 population trajectory established.
Natsuaki et al. (2009)	> 10,673	12-23	ADD Health	CES-D	MLM	7	3	2 trajectories for just depressive symptoms, 1 for males and 1 for females. 4 trajectories for dating. 6 trajectories for pubertal timing.
Needham (2007)	10828	11-18	ADD Health	CES-D	LGM	7	3	1 population trajectory established.

Needham (2012)	8322	11-24	ADD Health	CES-D	LGM	13	4	1 population trajectory established.
Rawana and Morgan (2014)	4359	12-21	NLSCY	CES-D	MLM	12	7	2 trajectories for depressive symptoms. 2 trajectories for low self-esteem.
St Clair et al. (2012)	905; 1208	12-16; 14-17	CHAMP; ROOTS	MFQ	Multi-level mixed effects	1; 3	4; 3	4 trajectories, 2 for males and 2 for females.
Stapinski et al. (2013)	2508	12-18	Chilean Adolescents	BDI	LGM	1.5	3	6 trajectories identified, 3 for males and 3 for females.
Wickrama et al. (2008)	458	15-25	FTP	SCL-90-R	LGM	10	7	1 population trajectory established.
Williams and Merten (2014)	1796	12-24	ADD Health	CES-D	LGM	12	4	1 population trajectory established.
Yip (2015)	146	13-16	American Adolescents	CES-D	MLM	3	9	4 trajectories identified for high/low discrimination and high/low sleep quality.

Table 3. A summary of individual population trajectory approaches studies examining trajectories of depressive symptoms from childhood to young adulthood. **ADD Health:** National Longitudinal Study of Adolescent Health, **ALSPAC:** Avon Longitudinal Study of Parents and Children, **BDI:** Beck Depression Inventory, **CDI:** Children's Depression Inventory, **CDRS-R:** Children's Depression Rating Scale-Revised, **CES-D:** Centre for Epidemiological Depression Scale, **CHAMP:** Cambridge Hormones and Moods Project, **FTP:** Family Transitions Project, **IYFP:** Iowa Youth and Families Project, **LCM:** Latent Curve Models, **LFGM:** Latent Factor Growth Model, **LGM:** Latent Growth Models, **LTA:** Latent Trajectory Analysis, **MFQ:** Mood and Feelings Questionnaire, **MLM:** Multilevel Modelling**, NLSCY:** National Longitudinal Survey of Children and Youth, **SCL-90-R:** Symptom-Checklist-90-Revised, **SES:** Socio-economic Status, **SEM:** Structural Equation Modelling, **SPQ:** Seattle Personality Questionnaire, **SMFQ:** Short Mood and Feelings Questionnaire.

Appendix 4 - Identifying Trajectories of Depressive Symptoms Across Adolescence and Young Adulthood

Appendix Table 4.1.

	Fractional Cubic Polynomial Model			Fractional Quartic Polynomial Model		
Parameter	Estimate	Std. Error	*p*-value	Estimate	Std. Error	*p*-value
β_0 - Intercept	6.123	0.056	<.001	6.312	0.058	<.001
β_1- Age (linear)	2.699	0.072	<.001	-89.581	4.449	<.001
β_2- Age^2 (quadratic)	-8.761	0.259	<.001	-96.614	4.474	<.001
β_3- Age^3 (cubic)	11.720	0.560	<.001	-41.152	1.995	<.001
β_4- Age^4 (quartic)	-	-	-	91.280	4.402	<.001
Intercept var	16.701	0.397	-	16.622	0.405	-
Intercept/slope cov	11.629	0.403	-	-245.720	19.286	-
Slope var	15.775	0.635	-	-708.725	53.201	-
Intercept/quadratic cov	-48.578	1.643	-	-289.810	19.756	-
Slope/quadratic cov	-43.476	2.056	-	731.261	46.095	-
Quadratic var	177.170	8.551	-	2271.649	132.106	-
Intercept/cubic cov	68.681	3.264	-	-104.083	8.591	-
Slope/cubic cov	28.371	3.401	-	-1061.195	126.071	-
Quadratic/cubic cov	-209.179	15.767	-	-366.232	114.373	-
Cubic var	407.060	37.840	-	-712.268	111.480	-
Intercept/quartic cov	-	-	-	256.117	19.178	-
Slope/quartic cov	-	-	-	356.829	26.318	-
Quadratic/quartic cov	-	-	-	-1098.660	65.067	-
Cubic/quartic cov	-	-	-	872.115	122.412	-
Quartic var	-	-	-	NIL	NIL	-
Residual variance	11.662	0.114	-	11.897	0.122	-
ICC		0.59			0.58	
Deviance		252728.57			252279.69	
AIC		252758.6			252319.7	
BIC		252889.8			252493.5	

Note: Var: Variance; Cov: Covariance; ICC: Intraclass correlation; AIC: Akaike information criterion; BIC: Bayesian information criterion. Model comparisons between the polynomials and fractional polynomials. Age was centered to 16.53. The 3rd order fractional polynomials takes the form of $\beta1x^2 + \beta2x^{-2}*\ln(x) + \beta3^{-2}*\ln(x)^2$, whilst the 4th order fractional polynomial takes the form of $\beta1x^2 + \beta2x^{-2}*\ln(x) + \beta3^2*\ln(x)^2 + \beta4^{-2}*\ln(x)^3$

Appendix 5 - Genetic and Environmental Risk Factors Associated with Trajectories of Depressive Symptoms from Adolescence to Young Adulthood.

Genotyping Information

Participants were genotyped using the Illumina HumanHap550 quad chip. Individuals were excluded based on gender mismatches, minimal or excessive heterozygosity, disproportionate levels of individual missingness (>3%), evidence of cryptic relatedness (>10% of alleles identical by descent), insufficient sample replication (IBD < 0.8) and being of non-European ancestry (assessed by multidimensional scaling analysis including HapMap 2 individuals). Thus, our analysis is only on individuals of European descent. SNPs with a minor allele frequency (MAF) of < 1%, Impute2 information quality metric of < 0.8, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium (P-value < 5e-7) were removed. Imputation performed using Impute v2.2.2 with the 1000 genomes reference panel (Phase 1, Version 3), using 2186 reference haplotypes. The maximum number of single nucleotide polymorphisms (snps) that were imputed (and passed filtering on MAF of > 1% and info score > 80%) was 8282911. In the case of siblings, one individual was dropped from analysis in order not to inflate the genetic effect, thus all results are based upon singletons.

Appendix Table 5.1. Showing Class Counts for the Latent Classes Based on Estimated Posterior Probabilities for Each Model.

	Childhood Persistent	Early-Adult Onset	Adolescent Limited	Childhood Limited	Stable low
5-Class Model Without Risk Factors or Confounders (n=9,394)	324 (3.5)	1086 (11.6)	880 (9.4)	480 (5.1)	6624 (70.5)
Unadjusted Univariate 5-Class Model (n=4,092)	106 (2.6)	461 (11.3)	393 (9.6)	241 (5.9)	2891 (70.7)
Adjusted Univariate 5-Class Model (n=3,525)	98 (2.8)	393 (11.1)	325 (9.2)	203 (5.8)	2506 (71.1)

% are given in parenthesis.

Appendix Table 5.2. Participant demographics for the 5-class trajectories model with no risk factors

	Childhood Persistent	Adolescent Limited	Early-Adult Onset	Childhood Limited	Stable Low	x^2, p
Sex (n=9,394)						
Males n (%)	54 (19.8)	232 (34.6)	203 (27.5)	177 (45.5)	3,829 (52.3)	$x^2 = 314.62$, $p = < .001$
Females n (%)	219 (80.2)	439 (65.4)	535 (72.5)	212 (54.5)	3,494 (47.7)	
Maternal Education (n=8,449)						
A Level or Higher n (%)	78 (32.0)	259 (42.3)	261 (39.1)	140 (40.4)	2,715 (41.3)	$x^2 = 14.09$, $p = .079$
O Level n (%)	89 (36.5)	217 (35.4)	252 (37.7)	124 (35.7)	2,298 (34.9)	
< O Level n (%)	77 (31.5)	137 (22.3)	155 (23.2)	83 (23.9)	1,564 (23.8)	
Maternal Socioeconomic Status (n=7,203)						
Professional/Managerial/Technical n (%)	73 (36.5)	201 (39.3)	227 (40.7)	103 (35.3)	2,336 (40.4)	$x^2 = 6.53$, $p = .163$
Skilled non-manual or lower n (%)	127 (63.5)	310 (60.7)	331 (59.3)	189 (64.7)	3,306 (58.6)	
Parity (n=8,528)						
First Born n (%)	95 (38.8)	288 (47.4)	299 (44.7)	166 (47.2)	3,070 (46.2)	$x^2 = 12.53$, $p = .129$
Second Born n (%)	91 (37.1)	220 (36.2)	229 (34.2)	124 (35.2)	2,377 (35.7)	
Third Born + n (%)	59 (24.1)	100 (16.4)	141 (21.1)	62 (17.6)	1,207 (18.4)	
Maternal Age At Pregnancy (n=8,872)						
< 25 Years n (%)	54 (21.0)	126 (19.7)	116 (16.7)	79 (21.7)	1,156 (16.7)	$x^2 = 18.31$, $p = .107$
25-29 n (%)	67 (26.1)	199 (31.2)	207 (29.9)	94 (25.8)	2,185 (31.6)	
30-34 n (%)	97 (37.7)	218 (34.2)	251 (36.2)	134 (36.8)	2,501 (36.1)	
35+ n (%)	39 (15.1)	95 (14.9)	119 (17.2)	57 (15.7)	1,078 (15.6)	

Pearson's chi-squared tests (x^2) used to highlight differences between participant demographics and the varying trajectories of depression symptoms.

No risk factors were included in this analysis.

Appendix Table 5.3. Participant demographics for the 5-class trajectories model with all risk factors included

	Childhood Persistent	Adolescent Limited	Early-Adult Onset	Childhood Limited	Stable Low	x^2, p
Sex (n=4,092)						
Males n (%)	23 (23.7)	113 (39.8)	87 (26.8)	84 (44.9)	1,729 (54)	x^2 = 130.74, p = < .001
Females n (%)	74 (76.3)	171 (60.2)	237 (73.2)	103 (55.1)	1,471 (46)	
Maternal Education (n=4,041)						
A Level or Higher n (%)	37 (38.5)	144 (50.9)	154 (48)	88 (48.1)	1,477 (46.8)	x^2 = 8.62, p = .375
O Level n (%)	35 (36.5)	94 (33.2)	119 (37.1)	60 (32.8)	1,108 (35.1)	
< O Level n (%)	24 (25.0)	45 (15.9)	48 (14.9)	35 (19.1)	573 (18.1)	
Maternal Socioeconomic Status (n=3,567)						
Professional/Managerial/Technical n (%)	36 (40.9)	113 (45.9)	135 (48.9)	69 (43.7)	1,265 (45.2)	x^2 = 2.35, p = .671
Skilled non-manual or lower n (%)	52 (59.1)	133 (54.1)	141 (51.1)	89 (56.3)	1,534 (54.8)	
Parity (n=4,034)						
First Born n (%)	38 (39.2)	129 (46.2)	139 (43.6)	87 (47.0)	1,476 (46.8)	x^2 = 4.95, p = .763
Second Born n (%)	41 (42.3)	104 (37.3)	115 (36)	65 (35.2)	1,140 (36.1)	
Third Born + n (%)	18 (18.6)	46 (14.5)	65 (20.4)	33 (17.8)	538 (17.1)	
Maternal Age At Pregnancy (n=4,092)						
< 25 Years n (%)	15 (15.5)	33 (11.6)	30 (16.2)	29 (15.5)	380 (11.9)	
25-29 n (%)	26 (26.8)	86 (30.3)	100 (30.9)	48 (25.7)	973 (30.4)	x^2 = 9.16, p = .689
30-34 n (%)	38 (39.2)	120 (42.2)	135 (41.7)	71 (38.0)	1,282 (40.1)	
35+ n (%)	18 (18.6)	45 (15.9)	59 (18.2)	39 (20.9)	565 (17.7)	

Pearson's chi-squared tests (x^2) used to highlight differences between participant demographics and the varying trajectories of depression symptoms for individuals with all the risk factors.

Risk factors included in this analysis were: sex, the polygenic risk score for depressive symptoms (PRS), postnatal depression, cruelty to the mother, childhood anxiety and bullied at age 10.

Appendix Table 5.4. Matrix of correlations between risk factors (n=3,525).

	Sex	Polygenic Risk Score	Postnatal Depression	Cruelty to Mother	Anxiety	Bullied
Sex	1	.	.	.	.	.
Polygenic Risk Score	-0.015 (P = 0.36)[c]	1	.	.	.	.
Postnatal Depression	0.016 (P = 0.66)[b]	0.032 (P = 0.06)[c]	1	.	.	.
Cruelty to Mother	-0.018 (P = 0.60)[b]	0.039 (P = 0.02)[c]	0.322 (P < 0.001)[b]	1	.	.
Anxiety	0.017 (P = 0.33)[c]	0.016 (P = 0.33)[a]	0.125 (P < 0.001)[c]	0.067 (P < 0.001)[c]	1	.
Bullied at Age 10	-0.147 (P < 0.001)[b]	0.048 (P = 0.005)[c]	0.095 (P = 0.02)[b]	0.142 (P = 0.002)[b]	0.06 (P = 0.001)[c]	1

Correlations presented with P values for correlations in parenthesis.

Sex was coded as 0 for males and 1 for females. The PRS was standardised to have a mean of 0 and a SD of 1. Postnatal depression, cruelty to mother and bullied at age 10 were coded as 0 for no and 1 for yes. Anxiety was coded between 0-12, with greater scores corresponding to worse childhood anxiety.

[a] Analysis was conducted using Pearson's correlations.

[b] Analysis was conducted using Tetrachoric correlations.

[c] Analysis was conducted using Point-Biserial correlations and verified using Pearson's correlations.

Appendix Table 5.5. Adjusted Univariate Associations Between All Risk Factors and Trajectories of Depressive Symptoms.

	Multinomial Odds Ratios (ORs) [Lower, Upper 95% CIs]				
	Childhood persistent vs. Stable low	Early-adult onset vs. Stable low	Adolescent limited vs. Stable low	Childhood-limited vs. Stable low	Omnibus *P*-value
Sex (n=9,394)[a]					
Female	6.13 [3.92, 9.58]	2.49 [1.97, 3.14]	4.5 [3.33, 6.07]	1.28 [0.96, 1.7]	<.001
Genetics (n=6,309)[a]					
Polygenic Risk Score	1.53 [1.27, 1.84]	1.2 [1.04, 1.38]	1.09 [0.94, 1.27]	1.04 [0.89, 1.23]	<.001
Early Life (n=6,345)[b]					
Postnatal Depression	2.14 [1.28, 3.57]	1.99 [1.35, 2.94]	1.2 [0.72, 1.99]	1.87 [1.17, 2.99]	<.001
Cruelty to Mother 2-4 Years	1.91 [1.16, 3.16]	1.73 [1.05, 2.85]	1.78 [1.2, 2.63]	1.3 [0.8, 2.12]	<.001
Childhood (n=4,733)[c]					
Anxiety at 7.6 Years	1.35 [1.22, 1.5]	1.14 [1.04, 1.24]	1.13 [1.03, 1.24]	1.22 [1.08, 1.37]	<.001
Bullied at 10 Years	4.94 [2.84, 8.6]	1.69 [1.15, 2.5]	1.89 [1.22, 2.91]	7.58 [5.0, 11.51]	<.001

[a] Analysis was not adjusted for any confounders or risk factors.

[b] Analysis included postnatal depression and cruelty to mother and the following confounders: biological sex, maternal age at birth, maternal socioeconomic status at birth, maternal educational attainment at birth and parity.

[c] Analysis included anxiety and bullying and was adjusted for the following confounders: biological sex, maternal age at birth, maternal socioeconomic status at birth, maternal educational attainment at birth and parity.

Appendix Table 5.6. Unadjusted Multivariate Associations Between All Risk Factors and Trajectories of Depressive Symptoms (n=4,092).

	Multinomial Odds Ratios (ORs) [Lower, Upper 95% CIs][a]				
	Childhood persistent vs. Stable low	Early-adult onset vs. Stable low	Adolescent limited vs. Stable low	Childhood-limited vs. Stable low	Omnibus *P*-value
Sex					
Female	6.09 [2.91, 12.74]	2.22 [1.55, 3.19]	5.9 [3.6, 9.66]	1.88 [1.23, 2.89][*]	<.001
Genetics					
Polygenic Risk Score	1.54 [1.16, 2.02]	1.28 [1.08, 1.52]	1.12 [0.93, 1.35]	1.05 [0.86, 1.28]	.002
Early Life					
Postnatal Depression	2.56 [1.3, 5.02]	1.98 [1.2, 3.28]	1.18 [0.64, 2.2]	1.69 [0.9, 3.18]	.008
Cruelty to Mother 2-4 Years	1.82 [0.82, 4.05][*]	2.17 [1.36, 3.46]	2.13 [1.33, 3.42]	1.07 [0.54, 2.12]	<.001
Childhood					
Anxiety at 7.6 Years	1.26 [1.12, 1.4]	1.12 [1.02, 1.23]	1.1 [1, 1.21]	1.27 [1.14, 1.41]	<.001
Bullied at 10 Years	4.23 [2.27, 7.89]	1.71 [1.12, 2.6]	1.37 [0.84, 2.25][*]	7.55 [4.86, 11.71]	<.001

[a] Analysis was not adjusted for any confounders.

[*] Indicates a substantive difference from the univariate model.

Appendix 6 - Identifying Critical Points of Trajectories of Depressive Symptoms from Childhood to Young Adulthood

Model equation

Reconsider equation 1 in the manuscript:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 x_{1j} + \beta_5 x_{1j} t_{ij} + \beta_6 x_{1j} t_{ij}^2 + \beta_7 x_{1j} t_{ij}^3 + u_{0j} + u_{1j} t_{ij} + u_{2j} t_{ij}^2 + u_{3j} t_{ij}^3 + e_{ij}$$

(Appendix equation 1)

where y_{ij} is the depressive symptom score and t_{ij} is the age (centred around 16 years, the approximate sample mean) for individual j at occasion i, x_{1j} is a dummy variable for being female, and u_{0j}, u_{1j}, u_{2j}, and u_{3j} are the random linear, quadratic and cubic effects, respectively, and e_{ij} is the occasion-specific residual.

Predicted depressive symptom scores

The predicted depressive symptom score for individual j at occasion i is given by

$$\hat{y}_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 x_{1j} + \beta_5 x_{1j} t_{ij} + \beta_6 x_{1j} t_{ij}^2 + \beta_7 x_{1j} t_{ij}^3 + u_{0j} + u_{1j} t_{ij} + u_{2j} t_{ij}^2 + u_{3j} t_{ij}^3$$

(Appendix equation 2)

The mean male and female predicted depressive symptom score at a given age t_{ij} can be obtained by setting all random effects to 0 and by setting x_{1j} to 0 or 1 accordingly.

Velocity

Differentiating appendix equation 1 with respect to t_{ij} gives the velocity (rate of change) in depressive symptoms

$$\frac{\partial y_{ij}}{\partial t_{ij}} = \beta_1 + 2\beta_2 t_{ij} + 3\beta_3 t_{ij}^2 + \beta_5 x_{1j} + 2\beta_6 x_{1j} t_{ij} + 3\beta_7 x_{1j} t_{ij}^2 + u_{1j} + 2u_{2j} t_{ij} + 3u_{3j} t_{ij}^2$$

(Appendix equation 3)

The mean male and female velocities at a given age t_{ij} can be obtained by setting all random effects to 0 and by setting x_{1j} to 0 or 1 accordingly.

Acceleration

Differentiating appendix equation 1 twice with respect to t_{ij} gives the acceleration in depressive symptoms

$$\frac{\partial^2 y_{ij}}{\partial t_{ij}^2} = 2\beta_2 + 6\beta_3 t_{ij} + 2\beta_6 x_{ij} + 6\beta_7 x_{ij} t_{ij} + 2u_{2j} + 6u_{3j} t_{ij}$$

(Appendix equation 4)

The mean male and female accelerations at a given age t_{ij} can be obtained by setting all random effects to 0 and by setting x_{1j} to 0 or 1 accordingly.

Age of peak velocity

Setting appendix equation 4 to zero and rearranging gives the age of peak velocity of depressive symptoms:

$$t_{ij,\text{APV}} = -\frac{2\beta_2 + 2\beta_6 x_{1j} + 2u_{2j}}{6\beta_3 + 6\beta_7 x_{1j} + 6u_{3j}}$$

(Appendix equation 5)

The predicted depressive symptom scores evaluated at $t_{ij,\text{APV}}$ can be found by substituting $t_{ij,\text{APV}}$ into appendix equation 2.

The mean male and female ages of peak velocity can be obtained by setting all random effects to 0 and by setting x_{1j} to 0 or 1 accordingly.

Age of maximum depressive symptoms

Setting appendix equation 3 equal to zero and rearranging using the quadratic formulae gives the age of the two turning points (i.e., age at minimum and age at maximum depressive symptoms.

$$t_{ij,\text{AMDS}} = \frac{-2(\beta_2 + \beta_6 x_{1j} + u_{2j}) \pm \sqrt{4\left(\beta_2 + \beta_6 x_{1j} + u_{2j}\right)^2 - 12\left(\beta_1 + \beta_5 x_{1j} + u_{1j}\right)\left(\beta_3 + \beta_7 x_{1j} + u_{3j}\right)}}{6\left(\beta_3 + \beta_7 x_{1j} + u_{3j}\right)}$$

(Appendix equation 6)

The predicted depressive symptom scores evaluated at the two values of $t_{ij,\mathrm{AMDS}}$ can be found by substituting the two values into Appendix equation 2.

The mean male and female ages of maximum depressive symptoms can be obtained by setting all random effects to 0 and by setting x_{1j} to 0 or 1 accordingly.

Covariates

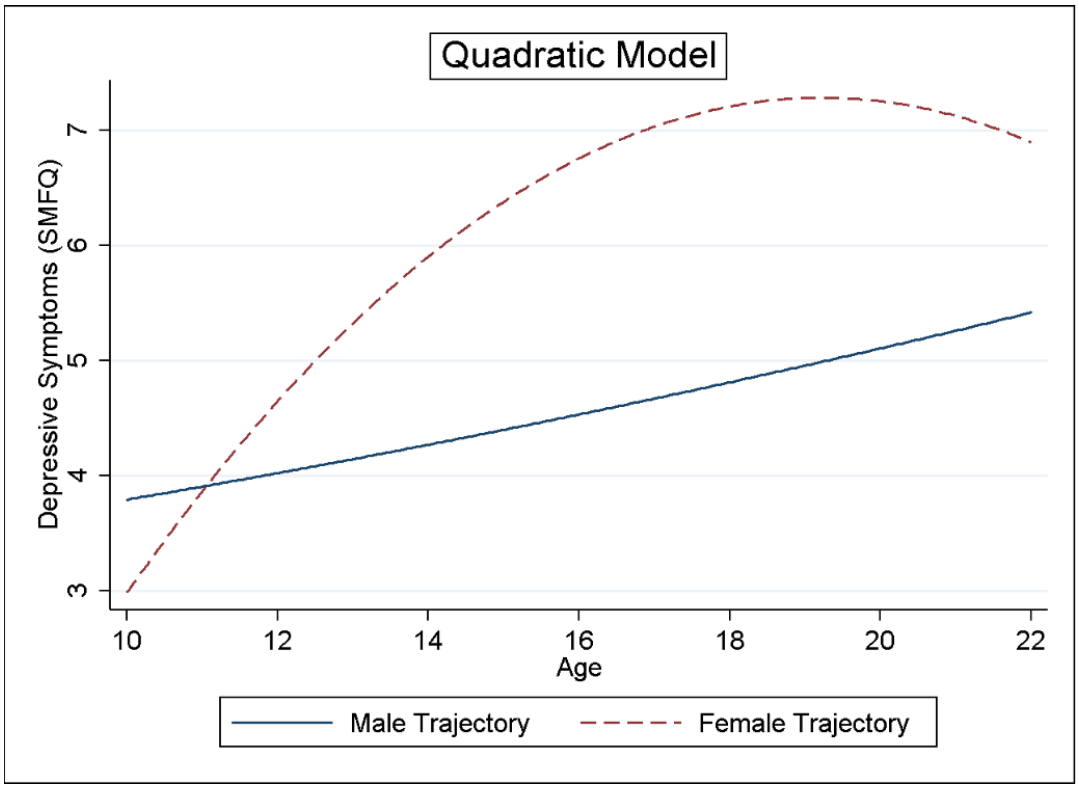
Covariates were included based upon previous evidence from the depressive symptoms literature that highlight correlations between depressive symptoms and missing data (Kingsbury et al., 2016; Mahedy et al., 2017; Pearson et al., 2017). These covariates were completed by the participant's main carer and assessed during the antenatal period. These included: maternal education (coded as 'A-level or higher', 'O-level' or '<O-level'), maternal social class (coded as 'Professional occupations or managerial and technical occupations' or 'Skilled non-manual occupations, skilled manual occupations, partly-skilled occupations and unskilled occupations', parity (whether the study child was 1st/2nd/3rd born or greater), housing tenure (coded as 'Mortgaged or owned', 'Privately rented' or 'Subsided rented'), financial difficulties (yes/no), maternal smoking in pregnancy (yes/no), maternal prenatal depression (yes/no) and maternal postnatal depression (yes/no). A binary indicator of the SMFQ source was also included as a covariate (clinic/questionnaire).

Our results were robust to the inclusion of these covariates that are associated with missing data (see Appendix tables 3-7 and Appendix figure 4). The total sample that included all the covariates was 6,097 individuals, resulting in 27,952 measurements (12,362 male/15,590 female).

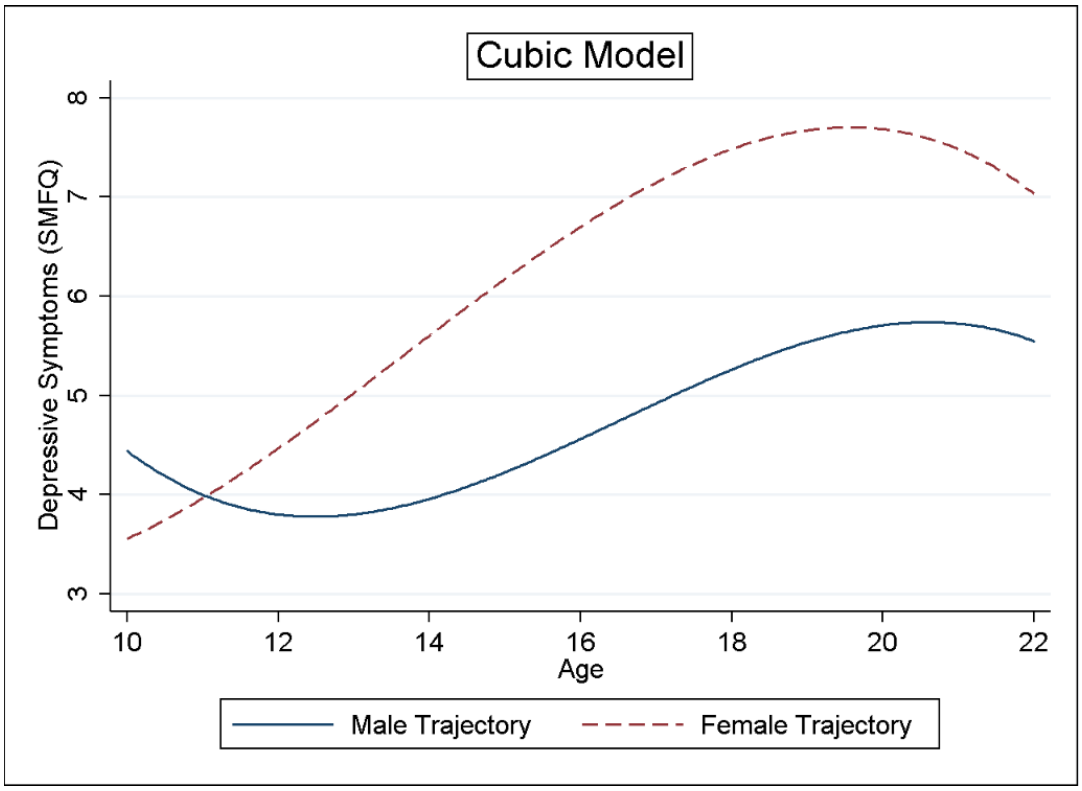
	Quadratic			Cubic			Quartic		
Parameter	Estimate	Std. Error	*p*-value	Estimate	Std. Error	*p*-value	Estimate	Std. Error	*p*-value
β_0 - Intercept	4.538	0.069	<.001	4.568	0.069	<.001	4.736	0.082	<.001
β_1- Age (slope)	0.135	0.01	<.001	0.357	0.022	<.001	0.361	0.022	<.001
β_2- Age^2 (acceleration)	0.002	0.002	0.308	0.012	0.002	<.001	-0.026	0.009	0.003
β_3- Age^3 (cubic change)	-	-	-	-0.007	0.001	<.001	-0.009	0.001	<.001
β_4- Female	2.222	0.095	<.001	2.132	0.095	<.001	2.328	0.112	<.001
β_5- FemalexAge	0.191	0.013	<.001	0.135	0.03	<.001	0.169	0.031	<.001
β_6- FemalexAge^2	-0.053	0.003	<.001	-0.051	0.003	<.001	-0.099	0.012	<.001
β_7- FemalexAge^3	-	-	-	0.002	0.001	0.036	0.001	0.0002	<.001
β_8- Age^4 (quartic change)	-	-	-	-	-	-	0.001	0.0003	<.001
β_9- FemalexAge^4	-	-	-	-	-	-	-0.001	0.001	0.335
Intercept variance	12.2	0.294	-	11.9335	0.2918	-	14.431	0.3885	-
Intercept/Slope covariance	0.773	0.03	-	1.2169	0.0623	-	1.3367	0.0736	-
Slope variance	0.115	0.005	-	0.4675	0.0275	-	0.5171	0.0281	-
Intercept/Quadratic covariance	-0.149	0.007	-	-0.1172	0.0076	-	-0.4715	0.033	-
Slope/Quadratic covariance	-0.004	0.001	-	-0.0055	0.002	-	-0.0243	0.0073	-
Quadratic variance	0.003	0.0003	-	0.0023	0.0003	-	0.0363	0.0038	-
Intercept/Cubic covariance	-	-	-	-0.0163	0.0017	-	-0.0282	0.0023	-
Slope/Cubic covariance	-	-	-	-0.008	0.0007	-	-0.0101	0.0008	-
Quadratic/Cubic covariance	-	-	-	0.0003	0.0001	-	0.0013	0.0003	-
Cubic variance	-	-	-	0.0001	0.00002	-	0.0002	0.00003	-
Intercept/Quartic covariance	-	-	-	-	-	-	0.0079	0.0007	-
Slope/Quartic covariance	-	-	-	-	-	-	0.0005	0.0002	-
Quadratic/Quartic covariance	-	-	-	-	-	-	-0.0006	0.0001	-
Cubic/Quartic covariance	-	-	-	-	-	-	-0.00002	0.00001	-
Quartic variance	-	-	-	-	-	-	0.00001	0.000002	-
Female residual variance	14.481	0.173	-	13.69	0.174	-	13.038	0.175	-
Male residual variance	9.765	0.141	-	9.332	0.149	-	8.899	0.151	-
Female/Male Variance *P* Wald-Test		<.001			<.001			<.001	
ICC		0.55			0.56			0.62	
Deviance		228583.53			227890.58			227532	
AIC		228611.5			227930.6			227586.5	
BIC		228731.9			228102.5			227818.6	

Appendix Table 1. Model comparisons between the quadratic, cubic and quartic models.

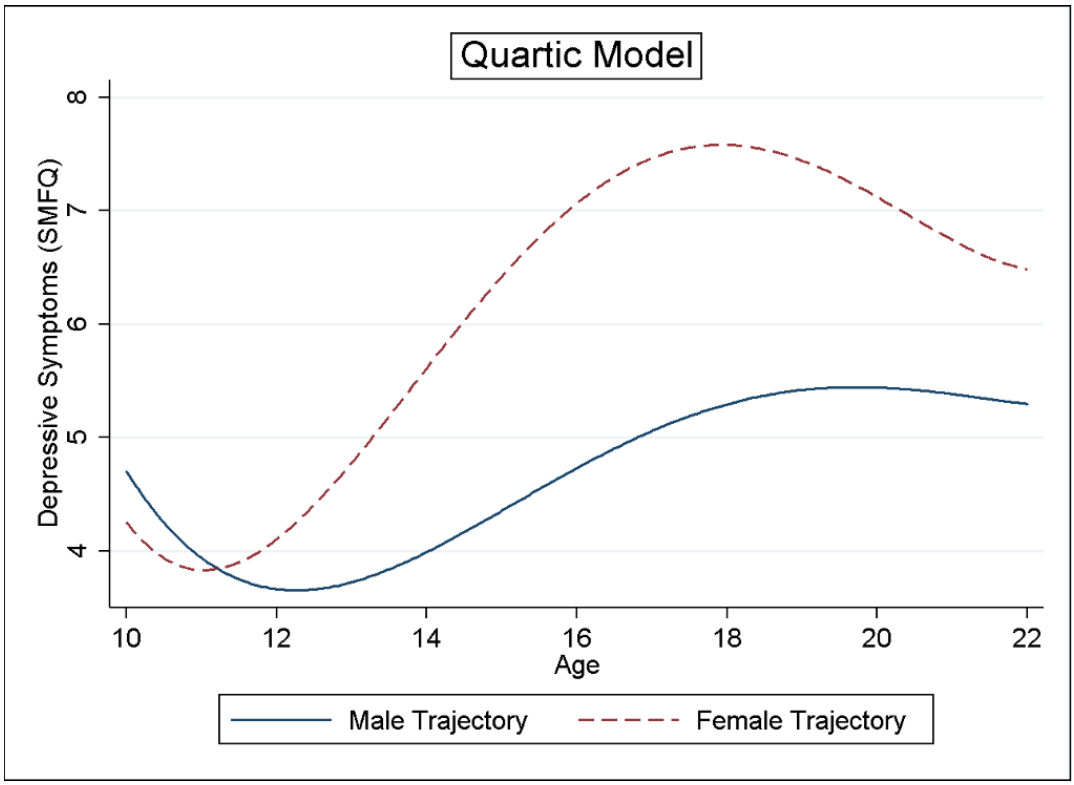
Appendix figure 1. The quadratic model for males and females.



Appendix figure 2. The cubic model for males and females



Appendix figure 3. The quartic model for males and females.



	Unadjusted Model (n=9,301)			Adjusted Model (n=6,097)		
Parameter	Estimate	Std. Error	*p*-value	Estimate	Std. Error	*p*-value
β_0 - Intercept	4.568	0.069	<.001	3.997	0.113	<.001
β_1- Age (slope)	0.357	0.022	<.001	0.380	0.027	<.001
β_2- Age^2 (acceleration)	0.012	0.002	<.001	0.013	0.003	<.001
β_3- Age^3 (cubic change)	-0.007	0.001	<.001	-0.007	0.001	<.001
β_4- Female	2.132	0.095	<.001	1.99	0.112	<.001
β_5- FemalexAge	0.135	0.03	<.001	0.129	0.036	<.001
β_6- FemalexAge^2	-0.051	0.003	<.001	-0.051	0.004	<.001
β_7- FemalexAge^3	0.002	0.001	0.036	0.001	0.001	0.148
Measurement	-	-	-	0.252	0.073	0.001
Mat Edu - O Level	-	-	-	-0.019	0.097	0.842
Mat Edu - <O Level	-	-	-	-0.161	0.121	0.181
Mat Sclass - III-V	-	-	-	-0.053	0.091	0.563
2nd Born	-	-	-	0.012	0.085	0.887
3rd Born+	-	-	-	0.355	0.114	0.002
Housing - Private Rented	-	-	-	0.317	0.184	0.085
Housing - Subsidised Rented	-	-	-	0.291	0.164	0.076
Financial Difficulties	-	-	-	0.595	0.101	<.001
Smoked During Pregnancy	-	-	-	0.829	0.11	<.001
Depression Pre-Pregnancy	-	-	-	0.641	0.119	<.001
Depression Post-Pregnancy	-	-	-	0.403	0.131	0.002
Intercept variance	11.9335	0.2918	-	11.1721	0.3315	-
Intercept/Slope covariance	1.2169	0.0623	-	1.0772	0.0707	-
Slope variance	0.4675	0.0275	-	0.4458	0.0314	-
Intercept/Quadratic covariance	-0.1172	0.0076	-	-0.1197	0.0088	-
Slope/Quadratic covariance	-0.0055	0.0020	-	-0.0044	0.0024	-
Quadratic variance	0.0023	0.0003	-	0.0026	0.0004	-
Intercept/Cubic covariance	-0.0163	0.0017	-	-0.0129	0.0019	-
Slope/Cubic covariance	-0.008	0.0007	-	-0.0075	0.0008	-
Quadratic/Cubic covariance	0.0003	0.0001	-	0.0002	0.0001	-
Cubic variance	0.0001	0.00002	-	0.0001	0.00002	-
Female residual variance	13.69	0.174	-	13.175	0.2	-
Male residual variance	9.332	0.149	-	9.372	0.175	-
Female/Male Variance *P* Wald-Test		<.001			<.001	
ICC		0.56			0.54	
Deviance		227890.58			158562.55	
AIC		227930.6			158626.5	
BIC		228102.5			158890.2	

Appendix Table 2. Full regression coefficients and variances for the unadjusted and adjusted cubic models.

	Unadjusted Model (n=5,409)			Adjusted Model (n=3,867)		
Parameter	Estimate	Std. Error	*p*-value	Estimate	Std. Error	*p*-value
β_0 - Intercept	4.471	0.082	<.001	3.955	0.126	<.001
β_1- Age (slope)	0.356	0.024	<.001	0.379	0.029	<.001
β_2- Age^2 (acceleration)	0.012	0.002	<.001	0.013	0.003	<.001
β_3- Age^3 (cubic change)	-0.007	0.001	<.001	-0.007	0.001	<.001
β_4- Female	2.090	0.110	<.001	1.977	0.126	<.001
β_5- FemalexAge	0.10	0.032	0.002	0.105	0.038	0.005
β_6- FemalexAge^2	-0.05	0.003	<.001	-0.05	0.004	<.001
β_7- FemalexAge^3	0.002	0.001	0.006	0.002	0.001	0.038
Measurement	-	-	-	0.25	0.075	0.001
Mat Edu - O Level	-	-	-	-0.127	0.113	0.26
Mat Edu - <O Level	-	-	-	-0.240	0.149	0.107
Mat Sclass - III-V	-	-	-	0.030	0.106	0.778
2nd Born	-	-	-	0.004	0.099	0.971
3rd Born+	-	-	-	0.379	0.139	0.006
Housing - Private Rented	-	-	-	0.570	0.2	0.011
Housing - Subsidised Rented	-	-	-	0.43	0.218	0.049
Financial Difficulties	-	-	-	0.442	0.124	<.001
Smoked During Pregnancy	-	-	-	0.758	0.137	<.001
Depression Pre-Pregnancy	-	-	-	0.745	0.147	<.001
Depression Post-Pregnancy	-	-	-	0.646	0.160	<.001
Intercept variance	11.3809	0.3123	-	10.6761	0.3485	-
Intercept/Slope covariance	1.1070	0.0651	-	0.9934	0.0732	-
Slope variance	0.4483	0.0277	-	0.4376	0.0316	-
Intercept/Quadratic covariance	-0.1093	0.0079	-	-0.1114	0.0091	-
Slope/Quadratic covariance	-0.004	0.002	-	-0.003	0.0024	-
Quadratic variance	0.0020	0.0003	-	0.0023	0.0004	-
Intercept/Cubic covariance	-0.0140	0.0018	-	-0.011	0.0020	-
Slope/Cubic covariance	-0.0077	0.0007	-	-0.0075	0.0008	-
Quadratic/Cubic covariance	0.0003	0.0001	-	0.0002	0.0001	-
Cubic variance	0.0001	0.00002	-	0.0001	0.00002	-
Female residual variance	13.567	0.183	-	13.083	0.208	-
Male residual variance	9.41	0.163	-	9.31	0.187	-
Female/Male Variance *P* Wald-Test		<.001			<.001	
ICC		0.55			0.54	
Deviance		183104.28			132101.03	
AIC		183144.3			132165	
BIC		183311.8			132422.9	

Appendix Table 3. Sensitivity analysis of full regression coefficients and variances for the unadjusted and adjusted cubic models with at least 4 measurements of SMFQ.

	Unadjusted (n=9,301)				Adjusted (n=6,097)			
	Males	Females	Difference	*p-value*	Males	Females	Difference	*p-value*
Intercept term for SMFQ	4.57 (0.07) [4.43, 4.7]	6.7 (0.07) [6.57, 6.83]	2.13 (0.09) [1.95, 2.32]	< 0.001	3.99 (0.11) [3.775, 4.218]	5.99 (0.11) [5.77, 6.20]	1.99 (0.11) [1.77, 2.21]	< 0.001
Linear term for SMFQ	0.36 (0.02) [0.31, 0.4]	0.49 (0.02) [0.45, 0.53]	0.14 (0.03) [0.08, 0.19]	< 0.001	0.379 (.027) [0.326, 0.433]	0.51 (0.03) [0.46, 0.56]	0.13 (0.04) [0.06, 0.2]	< 0.001
Quadratic term for SMFQ	0.01 (0.002) [0.008, 0.2]	-0.04 (0.002) [-0.05, -0.03]	0.05 (0.003) [0.05, 0.06]	< 0.001	0.013 (.003) [0.008, 0.018]	-0.04 (0.003) [-0.04, -0.032]	0.05 (0.004) [0.04, 0.06]	< 0.001
Cubic term for SMFQ	-0.007 (0.001) [-0.01, -0.006]	-0.01 (.001) [-0.001, -0.004]	0.002 (0.001) [0.0001, 0.003]	0.04	-0.007 (.001) [-0.01, -0.006]	-0.01 (0.001) [-0.01, -0.004]	0.001 (0.001) [0.0001, 0.003]	0.15

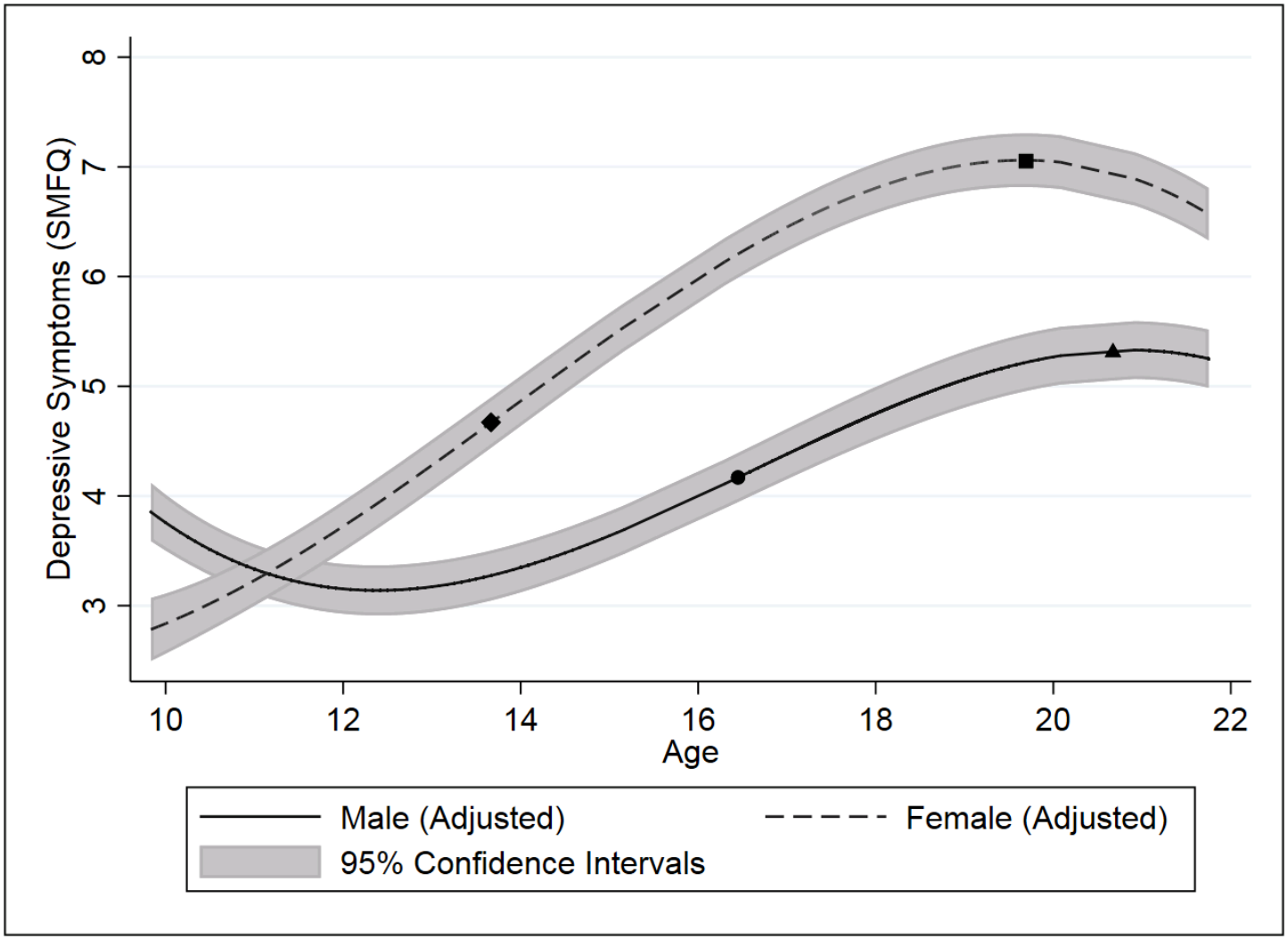
Appendix Table 4. Comparing parameter estimates and trajectories from the unadjusted and adjusted cubic models. The intercept was centered to age 16 for interpretability. The differences between each term were calculated as follows: the intercept term for males (β_0) *minus* the intercept term for females ($\beta_0 + \beta_4$), the linear term for males (β_1) *minus* the linear term for females ($\beta_1 + \beta_5$), the quadratic term for males (β_2) *minus* the quadratic term for females ($\beta_2 + \beta_6$), the cubic term for males (β_3) *minus* the cubic term for females ($\beta_3 + \beta_7$). Standard errors are given in (parenthesis), 95% confidence intervals are given in [parenthesis].

	Unadjusted (n=9,301)				Adjusted (n=6,097)			
	Males	Females	Difference	*p*-value	Males	Females	Difference	*p*-value
Age of Peak Velocity in SMFQ	16.36 (0.1) [16.18, 16.55]	13.51 (0.32) [12.88, 14.14]	2.86 (0.34) [2.2, 3.51]	< 0.001	16.44 (0.12) [16.21, 16.67]	13.66 (0.36) [12.97, 14.36]	2.78 (0.37) [2.05, 3.51]	< 0.001
Age of Maximum SMFQ	20.42 (0.14) [20.14, 20.69]	19.61 (0.5) [18.63, 20.6]	0.80 (0.55) [-0.27, 1.88]	0.14	20.68 (0.18) [20.32, 21.03]	19.68 (0.58) [18.54, 20.82]	.99 (0.65) [-0.28, 2.27]	0.13
SMFQ at Peak Velocity	4.76 (0.07) [4.62, 4.91]	5.42 (0.06) [5.30, 5.55]	0.66 (0.1) [0.47, 0.85]	< 0.001	4.24 (0.12) [4.01, 4.46]	4.77 (0.12) [4.54, 5.0]	0.54 (0.12) [0.31, 0.77]	< 0.001
SMFQ at Maximum Point	5.75 (0.1) [5.55, 5.95]	7.7 (0.09) [7.52, 7.88]	1.95 (0.14) [1.69, 2.22]	< 0.001	5.33 (0.13) [5.07, 5.59]	7.06 (0.13) [6.81, 7.30]	1.73 (0.16) [1.41, 2.04]	< 0.001

Appendix Table 5. Calculated features from the trajectories from the unadjusted and adjusted cubic models. Standard errors are given in (parenthesis), 95% confidence intervals are given in [parenthesis].

	Unadjusted (n=5,409)				Adjusted (n=3,867)			
	Males	Females	Difference	*p*-value	Males	Females	Difference	*p*-value
Age of Peak Velocity in SMFQ	16.358 (.106) [16.15, 16.566]	13.09 (.451) [12.206, 13.975]	3.267 (.464) [2.359, 4.176]	< 0.001	16.78 (.124) [16.536, 17.023]	13.702 (.473) [12.775, 14.63]	3.077 (.489) [2.119, 4.035]	< 0.001
Age of Maximum SMFQ	20.797 (.146) [20.51, 21.083]	20.519 (.684) [19.179, 21.859]	0.277 (.701) [-1.136, 1.691]	0.701	20.979 (.179) [20.629, 21.329]	20.528 (.756) [19.047, 22.01]	.451 (.81) [-1.136, 2.037]	0.578
SMFQ at Peak Velocity	4.527 (.083) [4.364, 4.69]	4.9 (.066) [4.766, 5.026]	0.369 (.106) [0.161, 0.577]	0.001	4.177 (.127) [3.928, 4.427]	4.564 (.127) [4.314, 4.813]	0.386 (.129) [0.133, 0.639]	0.003
SMFQ at Maximum Point	5.644 (.113) [5.423, 5.865]	7.407 (.098) [7.215, 7.6]	1.764 (.149) [1.471, 2.056]	< 0.001	5.258 (.146) [4.973, 5.544]	6.891 (.135) [6.627, 7.155]	1.633 (.171) [1.298, 1.968]	< 0.001

Appendix Table 6. Calculated features from the trajectories from the unadjusted and adjusted cubic models post sensitivity analysis (minimum of 4 measurements included). Standard errors are given in (parenthesis), 95% confidence intervals are given in [parenthesis].



Appendix figure 4. Adjusted population trajectories for males and females. SMFQ: Short Mood and Feelings Questionnaire. Features of the trajectories are overlaid with the following terms: ● Male age of peak velocity of depressive symptoms. ▲ Male age of maximum depressive symptoms. ♦ Female age of peak velocity of depressive symptoms. ■ Female age of maximum depressive symptoms.

Appendix 7 - Childhood Trauma and Trajectories of Depressive Symptoms Across Adolescence

Statistical Methods

Let y_{ij} denote the depressive symptom score for individual j at occasion i. The simplest trajectory model consists of a random intercept and a random quartic polynomial comprised of four age terms: age, age^2, age^3 and age^4. The model can then be written as:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4 + u_{0j} + u_{1j} t_{ij} + u_{2j} t_{ij}^2 + u_{3j} t_{ij}^3 + u_{4j} t_{ij}^4 + e_{ij}$$

(Appendix Equation 7.1)

where t_{ij} denotes the age in years (centred around 16.53 years, the mean age of all assessments) for that individual at that occasion, t_{ij}^2, t_{ij}^3, and t_{ij}^4, denote the quadratic, cubic and quartic age terms, and where $\beta_0, \beta_1, \beta_2, \beta_3, \beta_4$ denote the associated regression coefficients. The u_{0j}, u_{1j}, u_{2j}, u_{3j} and u_{4j} are the random intercept, linear, quadratic, cubic and quartic individual-specific effects, and e_{ij} is the occasion-specific residual.

The random effects are assumed multivariate normal distributed with zero mean vector and constant covariance matrix:

$$\begin{pmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \\ u_{4j} \end{pmatrix} \sim N\left\{ \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{u0}^2 & & & & \\ \sigma_{u01} & \sigma_{u1}^2 & & & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 & & \\ \sigma_{u03} & \sigma_{u13} & \sigma_{u23} & \sigma_{u3}^2 & \\ \sigma_{u04} & \sigma_{u14} & \sigma_{u24} & \sigma_{u34} & \sigma_{u4}^2 \end{pmatrix} \right\}$$

(Appendix Equation 7.2)

The elements of the covariance matrix summarise the degree to which individual-specific trajectories vary around the population-averaged trajectory. The residuals are assumed normally distributed with zero mean and constant variance:

$$e_{ij} \sim N(0, \sigma_e^2)$$

(Appendix Equation 7.3)

Predicted Depressive Symptom Trajectories

The model is therefore set up to predict both the population average trajectory

$$\mathrm{E}(y_{ij}|t_{ij}) = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4$$

(Appendix Equation 7.4)

and individual specific trajectories

$$\mathrm{E}(y_{ij}|t_{ij}, u_{0j}, u_{1j}, u_{2j}, u_{3j}, u_{4j}) = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4 + u_{0j} + u_{1j} t_{ij} + u_{2j} t_{ij}^2 + u_{3j} t_{ij}^3 + u_{4j} t_{ij}^4$$

(Appendix Equation 7.5)

Substituting the parameter estimates and the predicted random effect values into the above expression gives the population average and individual specific predicted depressive symptom scores.

Association Between Any Trauma and Depressive Symptom Trajectories

We ran a simple model to examine the association between any trauma (between the ages of 5-10) and subsequent trajectories of depressive symptoms. Let x_{1j} denote the presence ($x_{1j} = 1$) or absence ($x_{1j} = 0$) of trauma. The model can be written as:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4 + \beta_5 x_{1j} + \beta_6 x_{1j} t_{ij} + \beta_7 x_{1j} t_{ij}^2 + \beta_8 x_{1j} t_{ij}^3 + \beta_9 x_{1j} t_{ij}^4$$
$$+ u_{0j} + u_{1j} t_{ij} + u_{2j} t_{ij}^2 + u_{3j} t_{ij}^3 + u_{4j} t_{ij}^4 + e_{ij}$$

(Appendix Equation 7.6)

The population average trajectory becomes:

$$\mathrm{E}(y_{ij} | t_{ij}, x_{1j}) = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4 + \beta_5 x_{1j} + \beta_6 x_{1j} t_{ij} + \beta_7 x_{1j} t_{ij}^2 + \beta_8 x_{1j} t_{ij}^3 + \beta_9 x_{1j} t_{ij}^4$$

(Appendix Equation 7.7)

Thus, for individuals with no trauma we have

$$\mathrm{E}(y_{ij} | t_{ij}, x_{1j} = 0) = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4$$

(Appendix Equation 7.8)

While for individuals with trauma, and after some rearranging, we have

$$\mathrm{E}(y_{ij} | t_{ij}, x_{1j} = 1) = (\beta_0 + \beta_5) + (\beta_1 + \beta_6) t_{ij} + (\beta_2 + \beta_7) t_{ij}^2 + (\beta_3 + \beta_8) t_{ij}^3 + (\beta_4 + \beta_9) t_{ij}^4$$

(Appendix Equation 7.9)

Association Between Number of Traumas and Depressive Symptom Trajectories

We ran a second model to examine the association between the number of traumas (0, 1, 2, 3+) and trajectories of depressive symptoms. We decided to treat the number of traumas as a four-category ordinal variable, rather than as a linear variable as the difference in depressive symptoms between successive numbers of traumas may not increase linearly. First, we created three dummy variables corresponding to the number of traumas: 1 trauma, 2 traumas and 3 or more traumas. The dummy variables were then entered as main effects and as interactions with the four age terms of the quartic polynomial (i.e., number of traumas × intercept; number of traumas × age; number of traumas × age^2; number of traumas × age^3 and number of traumas × age^4). The intercept and the main effects of the quartic age polynomial therefore describe the no traumas group (i.e., the baseline or reference trajectory). For any give number of traumas, the corresponding dummy variable and interactions with the four age terms of the quartic age polynomial then describes how the trajectory for that trauma group deviates from that of the bassline no trauma group.

Let x_j denote the number of traumas (0, 1, 2, 3+) and x_{1j}, x_{2j}, x_{3j} the series of three dummy variables derived from this. The following table shows the relationship between the dummy variables and the original ordinal variable.

x_j	x_{1j}	x_{2j}	x_{3j}
0	0	0	0
1	1	0	0
2	0	1	0
3	0	0	1

When x_{1j} is set to 1 (x_{2j} and x_{3j} are set to 0), the model gives the trajectory with 1 trauma. When x_{2j} is set to 1 (x_{1j} and x_{3j} are set to 0), the model gives the 2 traumas trajectory and when x_{3j} is set to 1 (x_{1j} and x_{3j} are set to 0), the model gives the 3 or more traumas trajectories.

The depressive symptom score for individual j at occasion i is therefore given by:

$$
\begin{aligned}
y_{ij} &= \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4 \\
&+ \beta_5 x_{1j} + \beta_6 x_{1j} t_{ij} + \beta_7 x_{1j} t_{ij}^2 + \beta_8 x_{1j} t_{ij}^3 + \beta_9 x_{1j} t_{ij}^4 \\
&+ \beta_{10} x_{2j} + \beta_{11} x_{2j} t_{ij} + \beta_{12} x_{2j} t_{ij}^2 + \beta_{13} x_{2j} t_{ij}^3 + \beta_{14} x_{2j} t_{ij}^4 \\
&+ \beta_{15} x_{3j} + \beta_{16} x_{3j} t_{ij} + \beta_{17} x_{3j} t_{ij}^2 + \beta_{18} x_{3j} t_{ij}^3 + \beta_{19} x_{3j} t_{ij}^4 \\
&+ u_{0j} + u_{1j} t_{ij} + u_{2j} t_{ij}^2 + u_{3j} t_{ij}^3 + u_{4j} t_{ij}^4 + e_{ij}
\end{aligned}
$$

(Appendix Equation 7.10)

The population average depressive symptom score for each trauma group can then be obtained by setting all random effects to 0 and by setting the dummy variables to their relevant values as illustrated in the table above. An alternative way to visualise the population-average for each trajectory can be written as this:

0 Traumas: $E(y_{ij}|t_{ij}) = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4$

1 Trauma: $E(y_{ij}|t_{ij}, x_{0j} = 0,\ x_{1j} = 1,\ x_{2j} = 0,\ x_{3j} = 0) = (\beta_0 + \beta_5) + (\beta_1 + \beta_6)t_{ij} + (\beta_2 + \beta_7)t_{ij}^2 + (\beta_3 + \beta_8)t_{ij}^3 + (\beta_4 + \beta_9)t_{ij}^4$

2 Traumas: $E(y_{ij}|t_{ij}, x_{0j} = 0,\ x_{1j} = 0,\ x_{2j} = 1,\ x_{3j} = 0) = (\beta_0 + \beta_{10}) + (\beta_1 + \beta_{11})t_{ij} + (\beta_2 + \beta_{12})t_{ij}^2 + (\beta_3 + \beta_{13})t_{ij}^3 + (\beta_4 + \beta_{14})t_{ij}^4$

3+ Traumas: $E(y_{ij}|t_{ij}, x_{0j} = 0,\ x_{1j} = 0,\ x_{2j} = 0,\ x_{3j} = 1) = (\beta_0 + \beta_{15}) + (\beta_1 + \beta_{16})t_{ij} + (\beta_2 + \beta_{17})t_{ij}^2 + (\beta_3 + \beta_{18})t_{ij}^3 + (\beta_4 + \beta_{19})t_{ij}^4$

(Appendix Equation 7.11)

Calculating Depressive Symptoms Scores at Different Ages

To calculate and compare the varying depressive symptoms scores for the different trajectories, we first ran the model (i.e., the no trauma vs any trauma) to obtain the estimates from the two trajectories. The population averaged relationship conditional on the covariates is then given as follows:

$$\mathrm{E}(y_{ij}|t_{ij}, x_{1j}) = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4 + \beta_5 x_{1j} + \beta_6 x_{1j} t_{ij} + \beta_7 x_{1j} t_{ij}^2 + \beta_8 x_{1j} t_{ij}^3 + \beta_9 x_{1j} t_{ij}^4$$

(Appendix Equation 7.12)

This model can alternatively be written as:

No Trauma: $E(y_{ij}|t_{ij}, x_{1j} = 0) = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4$

Yes Trauma: $E(y_{ij}|t_{ij}, x_{1j} = 1) = (\beta_0 + \beta_5) + (\beta_1 + \beta_6) t_{ij} + (\beta_2 + \beta_7) t_{ij}^2 + (\beta_3 + \beta_8) t_{ij}^3 + (\beta_4 + \beta_9) t_{ij}^4$

(Appendix Equation 7.13)

As stated above, the intercept score was centred to around age 16.53. The expected outcome at age 16.53 is therefore given by

$$\mathrm{E}(y_{ij}|t_{ij} = 0, x_{1j}) = \beta_0 + \beta_5 x_{1j}$$

(Appendix Equation 7.14)

The any trauma variable was a dummy variable containing the values of 0/1 (with no trauma =0, and yes trauma =1), so the depressive symptoms score at age 16 for the no trauma trajectory would be the value of β_0 (or the reference category). The depressive symptoms score for the yes trajectory at age 16 would the take the value of β_0 + β_5 (the effect of no trauma [the baseline group] + the effect of trauma [the dummy].

Or written as follows:

$$depression_{age16j} = no\ trauma\ intercept + yes\ trauma\ intercept x_{1j}$$

(Appendix Equation 7.15)

We can sub in the estimates from the adjusted model in our model formula here where x_1 is 0 or 1:

$$depression_{age16} = 5.17 + 1.23x_{1j}$$

(Appendix Equation 7.16)

Therefore, if an individual had no trauma, their predicted score would equal just the no trauma intercept (β_0, 5.17). However, if an individual had trauma, their predicted depressive symptoms score at age 16 would be the no trauma intercept (β_0, 5.17) plus the yes trauma intercept (β_5, 1.23) = 6.4. We see from Table 2 and Table 4 in the manuscript that there is main effect of trauma on predicted depressive symptoms scores at age 16.

To calculate the depressive symptoms scores at different ages for the no trauma and yes trauma trajectories, we substituted the ages we wanted to investigate in for t_{ij} and 0/1 for the trauma dummy variable x_{1j}. In the main analysis in the manuscript, we calculated depressive symptoms scores at seven different ages (12, 14, 16, 18, 20, 22 and 24). To calculate the predicted depressive symptoms scores at age 12, we first calculated the mean centred age value to substitute for t_{ij} in our model (12 - 16.53 = -4.53). We ran the initial model (in supplementary equation 12) to obtain the estimates and then substituted in the values for β, t_{ij} and x_{1j}. For age 12 in the adjusted model, this took the following form where x_{1j} is 0 or 1:

$$depression_{age12j} = 5.17 + (0.32 \times -4.53) + (-0.10 \times -4.53^2) + (-0.004 \times -4.53^3) + (0.002 \times -4.53^4)$$

$$+1.23 \times x_{1j} + (0.06 \times x_{1j} \times -4.53) + (-0.001 \times x_{1j} \times -4.53^2) + (-0.001 \times x_{1j} \times -4.53^3) + (0.0001 \times x_{1j} \times -4.53^4)$$

(Appendix Equation 7.17)

Adding this up, we get the following results for the two different trajectories:

No Trauma Score at Age 12 = $\beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4$
No Trauma Score at Age 12 = 2.9
Yes Trauma at Age 12 = $(\beta_0 + \beta_5) + (\beta_1 + \beta_6)t_{ij} + (\beta_2 + \beta_7)t_{ij}^2 + (\beta_3 + \beta_8)t_{ij}^3 + (\beta_4 + \beta_9)t_{ij}^4$
Yes Trauma at Age 12 = 4.03

(Appendix Equation 7.18)

Finally, we used ‘nlcom’ in Stata to compare these scores to determine if there is a statistical difference in predicted depressive symptoms between these two trauma groups at age 12. ‘nlcom’ is a postestimation command that carries over additional information such as standard errors and confidence intervals when calculating postestimations, making it a useful tool for assessing multiple comparisons with levels of certainty.

We used the same format for the remaining ages as well as for the more complex model involving the number of traumas (0, 1, 2, 3+). For instance, to calculate the differences at age 22, we just substitute in the difference between 22 and 16.53 (5.47) in place of t_{ij}. The same format can easily be extended for models described in supplementary equations 17 and 18.

Appendix Tables

Appendix Table 7.1. Unadjusted Associations Between Any Trauma (between 5-10 Years) and SMFQ Trajectories (n=8,738)

	Direct Model Output			Alternative Parametrisation		
Parameter	Estimate	Std. Error	*p*-value	Estimate	Std. Error	*p*-value
β_0 No Trauma Intercept	5.75 [5.61, 5.90]	0.07	<.001	5.75 [5.61, 5.90]	0.07	<.001
β_1 No Trauma x Age	0.33 [0.30, 0.37]	0.02	<.001	0.33 [0.30, 0.37]	0.02	<.001
β_2 No Trauma x Age^2	-0.10 [-0.11, -0.09]	0.01	<.001	-0.1 [-0.11, -0.09]	0.01	<.001
β_3 No Trauma x Age^3	-0.005 [-0.01, -0.004]	0.0005	<.001	-0.005 [-0.01, -0.004]	0.0005	<.001
β_4 No Trauma x Age^4	0.002 [0.002, 0.002]	0.0001	<.001	0.002 [0.002, 0.002]	0.0001	<.001
β_5 Yes Trauma Intercept	1.36 [1.12, 1.60]	0.12	<.001	7.11 [6.92, 7.3]	0.12	<.001
β_6 Yes Trauma x Age	0.09 [0.03, 0.15]	0.03	0.003	0.42 [0.38, 0.47]	0.03	0.003
β_7 Yes Trauma x Age^2	-0.01 [-0.02, 0.01]	0.01	0.59	-0.1 [-0.12, 0.09]	0.01	0.59
β_8 Yes Trauma x Age^3	-0.002 [-0.003, -0.0004]	0.001	0.01	-0.007 [-0.008, -0.006]	0.001	0.01
β_9 Yes Trauma x Age^4	0.0002 [-0.0002, 0.001]	0.0002	0.33	0.002 [0.002, 0.002]	0.0002	0.33
Deviance	238151.27					

The no trauma variable should be viewed as the reference category as trauma was coded as a dummy variable (0/1). Thus, the intercept score (and subsequent age terms) for an individual with trauma would be no trauma intercept + yes trauma intercept (i.e., $\beta_0 + \beta_5$). The same applies for all age terms.

Appendix Table 7.2. Unadjusted Associations Between Number of Traumas (5-10 Years) and SMFQ Trajectories (n=8,872)

	Direct Model Output			Alternative Parametrisation		
Parameter	Estimate	Std. Error	*p*-value	Estimate	Std. Error	*p*-value
β_0 No Traumas Intercept	5.78 [5.64, 5.93]	0.07	<.001	5.78 [5.64, 5.93]	0.07	<.001
β_1 No Traumas x Age	0.33 [0.30, 0.37]	0.02	<.001	0.33 [0.30, 0.37]	0.02	<.001
β_2 No Traumas x Age^2	-0.10 [-0.11, -0.09]	0.01	<.001	-0.1 [-0.11, -0.09]	0.01	<.001
β_3 No Traumas x Age^3	-0.005 [-0.01, -0.004]	0.0005	<.001	-0.005 [-0.01, -0.004]	0.0005	<.001
β_4 No Traumas x Age^4	0.002 [0.002, 0.002]	0.0001	<.001	0.002 [0.002, 0.002]	0.0001	<.001
β_5 1 Trauma Intercept	0.81 [0.54, 1.08]	0.14	<.001	6.59 [6.36, 6.82]	0.12	<.001
β_6 1 Trauma x Age	0.05 [-0.02, 0.12]	0.03	0.15	0.38 [0.32, 0.44]	0.03	0.15
β_7 1 Trauma x Age^2	0.01 [-0.01, 0.03]	0.01	0.24	-0.08 [-0.1, -0.07]	0.01	0.24
β_8 1 Trauma x Age^3	-0.001 [-0.003, 0.0003]	0.001	0.11	-0.006 [-0.008, -0.005]	0.001	0.11
β_9 1 Trauma x Age^4	-0.0002 [-0.001, 0.0003]	0.0002	0.45	0.002 [0.001, 0.002]	0.0002	0.45
β_{10} 2 Traumas Intercept	1.9 [1.48, 2.32]	0.21	<.001	7.69 [7.29, 8.08]	0.21	<.001
β_{11} 2 Traumas x Age	0.15 [0.04, 0.25]	0.05	0.005	0.48 [0.38, 0.58]	0.05	0.005
β_{12} 2 Traumas x Age^2	-0.02 [-0.05, 0.01]	0.02	0.27	-0.12 [-0.14, -0.09]	0.02	0.27
β_{13} 2 Traumas x Age^3	-0.003 [-.0.01, -0.00005]	0.001	0.05	-0.007 [-.0.01, -0.005]	0.001	0.05
β_{14} 2 Traumas x Age^4	0.001 [-0.0001, 0.001]	0.0003	0.09	0.002 [0.002, 0.003]	0.0003	0.09
β_{15} 3+ Traumas Intercept	3.63 [3.01, 4.26]	0.32	<.001	9.42 [8.81, 10.03]	0.32	<.001
β_{16} 3+ Traumas x Age	0.23 [0.08, 0.39]	0.08	0.003	0.57 [0.42, 0.71]	0.08	0.003
β_{17} 3+ Traumas x Age^2	-0.09 [-0.14, -0.05]	0.02	<.001	-0.19 [-0.24, -0.14]	0.02	<.001
β_{18} 3+ Traumas x Age^3	-0.005 [-0.01, -0.001]	0.002	0.03	-0.009 [-0.01, -0.005]	0.002	0.03
β_{19} 3+ Traumas x Age^4	0.002 [0.001, 0.003]	0.0005	0.001	0.003 [0.002, 0.004]	0.0005	0.001
Deviance	239353.67					

The no traumas variable should be viewed as the reference category as the number of traumas were coded as dummy variable (0/1/2/3). Thus, the intercept score (and subsequent age terms) for an individual with 3+ traumas is the no trauma intercept + 3+ traumas intercept (i.e., $\beta_0 + \beta_{15}$). The same applies for all age terms. The standard error and p-value correspond to the differences between the trauma estimates and the no trauma differences.

Appendix 8 - Association Between Polygenic Risk and Trajectories of Depressive Symptoms

Methods

1. Genotyping Information

Participants were genotyped using the Illumina HumanHap550 quad chip. Individuals were excluded based on gender mismatches, minimal or excessive heterozygosity, disproportionate levels of individual missingness (>3%), evidence of cryptic relatedness (>10% of alleles identical by descent), insufficient sample replication (IBD < 0.8) and being of non-European ancestry (assessed by multidimensional scaling analysis including HapMap 2 individuals). Thus, our analysis is only on individuals of European descent. SNPs with a minor allele frequency (MAF) of < 1%, Impute2 information quality metric of < 0.8, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium (P-value < 5e-7) were removed. Imputation performed using Impute v2.2.2 with the 1000 genomes reference panel (Phase 1, Version 3), using 2186 reference haplotypes. The maximum number of single nucleotide polymorphisms (snps) that were imputed (and passed filtering on MAF of > 1% and info score > 80%) was 8282911. In the case of siblings, one individual was dropped from analysis in order not to inflate the genetic effect, thus all results are based upon singletons.

2. Negative Control Variables

Height in centimetres (cm) was measured at research clinics on eight occasions between ages 7 and 18. The methods for creating the PRS for height were identical to those listed above, except summary statistics for the height GWAS were based on 253,288 individuals (Wood et al., 2014), and the PRS was weighted on the effect sizes of 93,588 SNPs.

Statistical Methods

1. Negative Control Analysis

We ran negative control analysis between the height PRS and trajectories of depressive symptoms. Negative control exposures are used to examine whether observed associations are likely due to a bias that is expected to affect both the exposure and the control exposure, but where the control exposure should not affect the outcome. In this context, this was to ensure that the association between the depressive symptoms PRS and change in depressive symptoms was not due to analysing additional measures in a trajectories framework (i.e., change over time being a statistical artefact as a result of more power). We then ran additional analysis examining the association between the depressive symptoms PRS and height trajectories. Height trajectories were modelled using quadratic polynomial growth curve models.

2. Model Fit

Model fit for the trajectories were assessed using deviance, Akaike information criterion (AIC) and Bayesian information criterion (BIC), as recommended by (Singer & Willett, 2003). Briefly, lower deviance, AIC and BIC indicate better model fit. We examined model fit twice: on the first occasion we examined model fit for just those with at least one assessment of the SMFQ (Table S1). Next, we examined model fit for individuals with at least one SMFQ assessment and data on sex, principal components and genetic information (PRS) (Table S2). Both analyses indicted that a quartic polynomial model fitted the data the best. As a final check, we plotted all four models (linear, quadratic, cubic and quartic) over the descriptive data to visually compare the models. This once again indicated that that the quartic model was preferred (Figure S1).

Table S1. Comparisons between polynomial models with SMFQ data (n=9,399).

Model	**Deviance**	**AIC**	**BIC**
Linear Model	254892.8	254904.8	254957
Quadratic Polynomial	252509.6	253529.6	253616.5
Cubic Polynomial	253115	253145.5	253275.8
Quartic Polynomial	**252257.2**	**252299.2**	**252481.7**

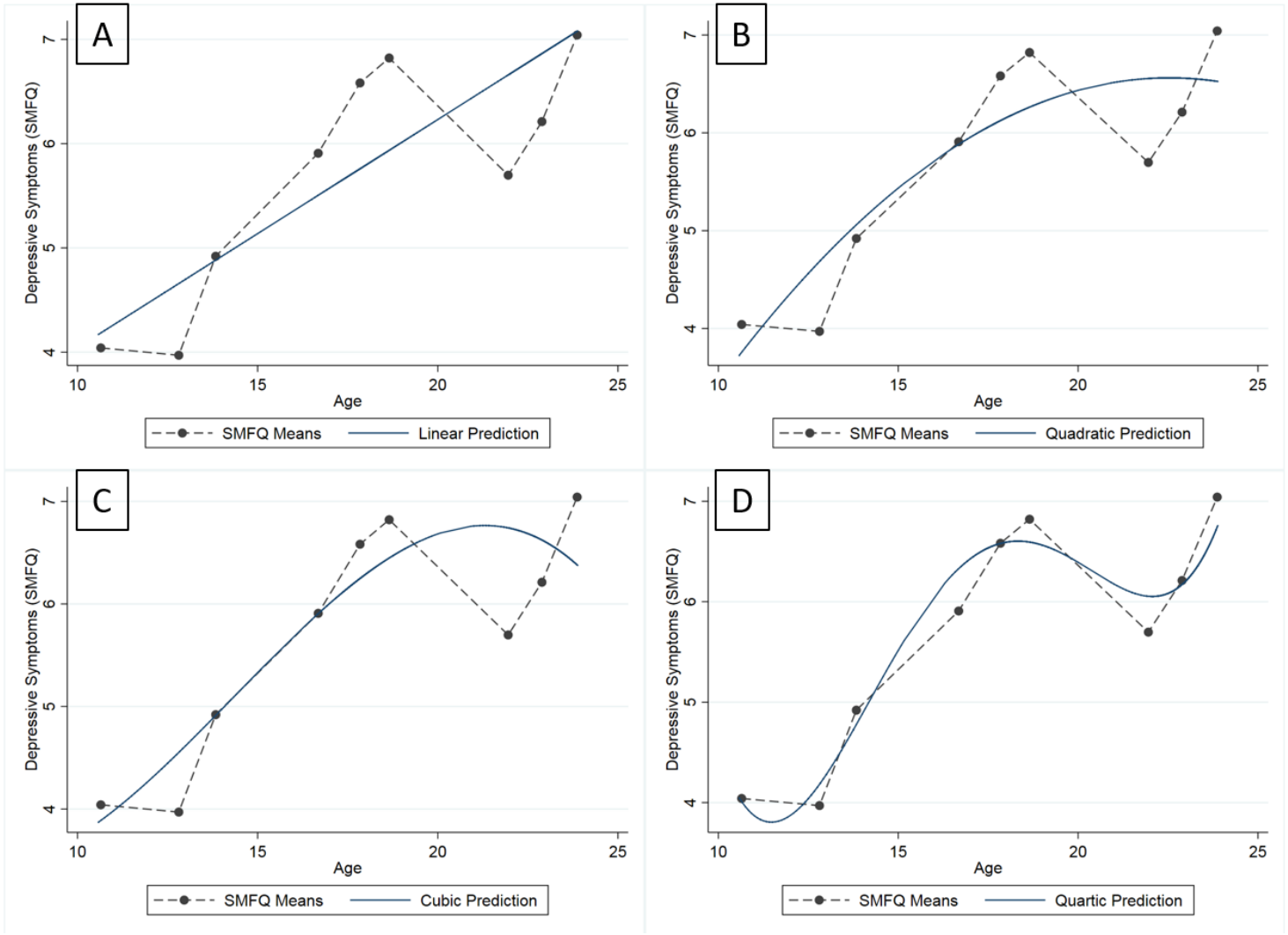
Model fit by the four polynomial models. SMFQ: short mood and feelings questionnaire; AIC: Akaike information criterion; BIC: Bayesian information criterion

Table S2. Comparisons between polynomial models with both SMFQ, sex, principal component and PRS data (n=6,305).

Model	**Deviance**	**AIC**	**BIC**
Linear Model	182364.65	182402.6	182561.5
Quadratic Polynomial	181419.9	181467.9	181668.6
Cubic Polynomial	181131.22	181191.2	181442.1
Quartic Polynomial	**180512.11**	**180586.1**	**180895.6**

Model fit by the four polynomial models. SMFQ: short mood and feelings questionnaire; AIC: Akaike information criterion; BIC: Bayesian information criterion

Figure S1. Comparisons between linear (A), quadratic (B), cubic (C) and quartic (D) models.



3. Model Equations

The quartic polynomial model that we chose to use can be denoted by the following equation:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4 + \beta_5 x_{1j} + \beta_6 x_{1j} t_{ij} + \beta_7 x_{1j} t_{ij}^2 + \beta_8 x_{1j} t_{ij}^3 + \beta_9 x_{1j} t_{ij}^4$$
$$+ u_{0j} + u_{1j} t_{ij} + u_{2j} t_{ij}^2 + u_{3j} t_{ij}^3 + u_{3j} t_{ij}^4 + e_{ij}$$

(Appendix equation 8.1)

where y_{ij} is the depressive symptom score and t_{ij} is the age (centred to 16.53 years, the approximate sample mean) for individual j at occasion i. Here β_0, β_1, β_2, β_3 and β_4 represent the intercept, linear, quadratic, cubic and quartic fixed effects respectively. x_{1j} is the standardised PRS, which in this equation represents a main effect of the PRS $\beta_5 x_{1j}$ followed by the interactions between the PRS and the linear ($\beta_6 x_{1j}$), quadratic ($\beta_7 x_{1j}$), cubic ($\beta_8 x_{1j}$) and quartic terms ($\beta_9 x_{1j}$). Also, u_{0j}, u_{1j}, u_{2j}, u_{3j} and u_{4j} are the random linear, quadratic, cubic and quartic effects that allow each individual to have their own unique trajectory that deviates from the population average. Finally, e_{ij} is the occasion-specific residual.

The random effects are assumed multivariate normal distributed with zero mean vector and constant covariance matrix:

$$\begin{pmatrix} u_{0j} \\ u_{1j} \\ u_{2j} \\ u_{3j} \\ u_{4j} \end{pmatrix} \sim N\left\{ \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{u0}^2 & & & & \\ \sigma_{u01} & \sigma_{u1}^2 & & & \\ \sigma_{u02} & \sigma_{u12} & \sigma_{u2}^2 & & \\ \sigma_{u03} & \sigma_{u13} & \sigma_{u23} & \sigma_{u3}^2 & \\ \sigma_{u04} & \sigma_{u14} & \sigma_{u24} & \sigma_{u34} & \sigma_{u4}^2 \end{pmatrix} \right\}$$

(Appendix equation 8.2)

The elements of the covariance matrix summarise the degree to which individual-specific trajectories vary around the population-averaged trajectory. The residuals are assumed normally distributed with zero mean and constant variance:

$$e_{ij} \sim N(0, \sigma_e^2)$$

(Appendix equation 8.3)

Predicted trajectories of depressive symptoms with the quartic polynomial growth curve model can therefore be defined in two ways:

To predict both the population average trajectory:

$$\mathrm{E}\left(y_{ij}\middle|t_{ij}\right) = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4$$

(Appendix equation 8.4)

and individual specific trajectories:

$$\mathrm{E}\left(y_{ij}\middle|t_{ij}, u_{0j}, u_{1j}, u_{2j}, u_{3j}, u_{4j}\right) = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4 + u_{0j} + u_{1j} t_{ij} + u_{2j} t_{ij}^2 + u_{3j} t_{ij}^3 + u_{4j} t_{ij}^4$$

(Appendix equation 8.5)

Substituting the parameter estimates and the predicted random effect values into the above expression gives the population average and individual specific predicted depressive symptom scores.

Likewise, to examine the association between the PRS and predicted trajectories of depressive symptoms with the quartic polynomial growth curve model, one overall model can be specified where x_{1j} is the standardised PRS and can be subbed into the equation:

$$\mathrm{E}(y_{ij}|t_{ij}, x_{1j}) = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + \beta_3 t_{ij}^3 + \beta_4 t_{ij}^4 + \beta_5 x_{1j} + \beta_6 x_{1j} t_{ij} + \beta_7 x_{1j} t_{ij}^2 + \beta_8 x_{1j} t_{ij}^3 + \beta_9 x_{1j} t_{ij}^4$$

(Appendix equation 8.6)

To examine differences between individuals with greater or less genetic liability, we ran a simple model to examine the association between a higher PRS (+1 SD) and a lower PRS (-1 SD) and subsequent trajectories of depressive symptoms. Let x_{1j} denote the higher PRS and can be multiplied by either 1 (+ SD) or -1 (-1 SD). The model can be written as:

High PRS: $E(y_{ij}|t_{ij}, x_{1j}) = (\beta_0 + \beta_5)*1 + (\beta_1 + \beta_6)t_{ij}*1 + (\beta_2 + \beta_7)t_{ij}^2*1 + (\beta_3 + \beta_8)t_{ij}^3*1 + (\beta_4 + \beta_9)t_{ij}^4*1$

Low PRS: $E(y_{ij}|t_{ij}, x_{1j}) = (\beta_0 + \beta_5)*-1 + (\beta_1 + \beta_6)t_{ij}*-1 + (\beta_2 + \beta_7)t_{ij}^2*-1 + (\beta_3 + \beta_8)t_{ij}^3*-1 + (\beta_4 + \beta_9)t_{ij}^4*-1$

(Appendix equation 8.7)

Results

3.5. Negative Control Analysis

Negative control analysis using a PRS for height found no association between the height PRSand depressive symptoms at the intercept age ($P = 0.753$), or an association with change over time ($Ps \geq 0.250$). Similar results were observed for the other negative control of the depressive symptoms PRS and trajectories of height ($Ps \geq 0.330$), all of which implying that any benefits from the repeated measures model were not only due to increase in statistical power.

Table S3 Association Between Depressive Symptoms PRS and Depressive Symptoms at Age 10.60 (N=5320)

PRS Threshold	Beta	95% CIs Low	95% CIs High	*P* value	FDR Adjusted *P* with 0.05 Level	ΔR^2
$5.00x10^{-08}$	0.056	-0.037	0.151	0.237	0.348	0.02%
$5.00\ x10^{-07}$	0.007	-0.100	0.086	0.887	0.939	0.00%
$5.00\ x10^{-06}$	0.013	-0.080	0.106	0.777	0.848	0.00%
$5.00\ x10^{-05}$	0.106	0.012	0.201	0.028	0.067	0.09%
$5.00\ x10^{-04}$	0.101	0.007	0.195	0.035	0.081	0.08%
$5.00\ x10^{-03}$	0.091	-0.003	0.185	0.057	0.121	0.06%
$5.00\ x10^{-02}$	0.088	-0.007	0.183	0.124	0.223	0.06%
$5.00\ x10^{-01}$	0.129	0.034	0.223	0.008	0.026	0.13%

PRS: Polygenic risk score; FDR: False Discovery rate. Incremental R2 (ΔR2) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models.

Table S4 Association Between Depressive Symptoms PRS and Depressive Symptoms at Age 12.80 (N=4928)

PRS Threshold	Beta	95% CIs Low	95% CIs High	*P* value	FDR Adjusted *P* with 0.05 Level	ΔR^2
$5.00x10^{-08}$	0.044	-0.151	0.063	0.416	0.565	0.01%
$5.00\ x10^{-07}$	0.038	-0.067	0.143	0.478	0.604	0.01%
$5.00\ x10^{-06}$	0.029	-0.136	0.077	0.593	0.689	0.00%
$5.00\ x10^{-05}$	0.023	-0.086	0.131	0.68	0.765	0.00%
$5.00\ x10^{-04}$	0.043	-0.064	0.150	0.434	0.568	0.01%
$5.00\ x10^{-03}$	0.145	0.038	0.252	0.008	0.024	0.14%
$5.00\ x10^{-02}$	0.146	0.039	0.254	0.008	0.025	0.14%
$5.00\ x10^{-01}$	0.210	0.102	0.317	0.0001	0.0008	0.29%

PRS: Polygenic risk score; FDR: False Discovery rate. Incremental R2 (ΔR2) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models.

Table S5 Association Between Depressive Symptoms PRS and Depressive Symptoms at Age 13.80 (N=4495)

PRS Threshold	Beta	95% CIs Low	95% CIs High	*P* value	FDR Adjusted *P* with 0.05 Level	ΔR^2
$5.00x10^{-08}$	0.051	-0.181	0.079	0.44	0.566	0.01%
$5.00\ x10^{-07}$	0.045	-0.081	0.172	0.482	0.598	0.01%
$5.00\ x10^{-06}$	0.063	-0.192	0.065	0.333	0.470	0.02%
$5.00\ x10^{-05}$	0.004	-0.128	0.137	0.948	0.975	0.00%
$5.00\ x10^{-04}$	0.189	0.059	0.319	0.004	0.016	0.18%
$5.00\ x10^{-03}$	0.163	0.034	0.292	0.013	0.035	0.13%
$5.00\ x10^{-02}$	0.093	-0.036	0.222	0.158	0.265	0.04%
$5.00\ x10^{-01}$	0.170	0.041	0.299	0.01	0.028	0.14%

PRS: Polygenic risk score; FDR: False Discovery rate. Incremental R2 (ΔR2) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models.

Table S6 Association Between Depressive Symptoms PRS and Depressive Symptoms at Age 16.70 (N=3524)

PRS Threshold	Beta	95% CIs Low	95% CIs High	*P* value	FDR Adjusted *P* with 0.05 Level	ΔR^2
$5.00x10^{-08}$	0.033	-0.147	0.214	0.716	0.793	0.00%
$5.00\ x10^{-07}$	0.064	-0.115	0.243	0.483	0.589	0.01%
$5.00\ x10^{-06}$	0.140	-0.041	0.320	0.129	0.227	0.06%
$5.00\ x10^{-05}$	0.112	-0.072	0.296	0.234	0.351	0.04%
$5.00\ x10^{-04}$	0.254	0.074	0.434	0.006	0.022	0.20%
$5.00\ x10^{-03}$	0.349	0.170	0.528	0.0001	0.0009	0.39%
$5.00\ x10^{-02}$	0.344	0.164	0.524	0.0002	0.001	0.37%
$5.00\ x10^{-01}$	0.304	0.125	0.483	0.001	0.005	0.29%

PRS: Polygenic risk score; FDR: False Discovery rate. Incremental R2 (ΔR2) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models.

Table S7 Association Between Depressive Symptoms PRS and Depressive Symptoms at Age 17.80 (N=3212)

PRS Threshold	Beta	95% CIs Low	95% CIs High	*P* value	FDR Adjusted *P* with 0.05 Level	ΔR^2
$5.00x10^{-08}$	0.022	-0.201	0.157	0.809	0.869	0.01%
$5.00\ x10^{-07}$	0.001	-0.185	0.168	0.924	0.964	0.00%
$5.00\ x10^{-06}$	0.002	-0.177	0.181	0.985	0.985	0.00%
$5.00\ x10^{-05}$	0.135	-0.047	0.317	0.147	0.252	0.07%
$5.00\ x10^{-04}$	0.242	0.062	0.422	0.009	0.026	0.21%
$5.00\ x10^{-03}$	0.364	0.186	0.543	0.00007	0.0008	0.49%
$5.00\ x10^{-02}$	0.371	0.192	0.550	0.00005	0.0007	0.50%
$5.00\ x10^{-01}$	0.413	0.236	0.591	$5.00x10^{-06}$	9.00E-05	0.64%

PRS: Polygenic risk score; FDR: False Discovery rate. Incremental R2 (ΔR2) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models.

Table S8 Association Between Depressive Symptoms PRS and Depressive Symptoms at Age 18.70 (N=2389)

PRS Threshold	Beta	95% CIs Low	95% CIs High	*P* value	FDR Adjusted *P* with 0.05 Level	ΔR^2
$5.00x10^{-08}$	0.190	-0.038	0.417	0.102	0.198	0.11%
$5.00\ x10^{-07}$	0.245	0.015	0.474	0.036	0.081	0.18%
$5.00\ x10^{-06}$	0.156	-0.073	0.384	0.181	0.290	0.07%
$5.00\ x10^{-05}$	0.054	-0.179	0.288	0.648	0.741	0.01%
$5.00\ x10^{-04}$	0.138	-0.089	0.365	0.233	0.357	0.06%
$5.00\ x10^{-03}$	0.453	0.225	0.681	0.0001	0.0007	0.61%
$5.00\ x10^{-02}$	0.311	0.083	0.539	0.007	0.024	0.29%
$5.00\ x10^{-01}$	0.339	0.109	0.568	0.004	0.015	0.34%

PRS: Polygenic risk score; FDR: False Discovery rate. Incremental R2 (ΔR2) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models.

Table S9 Association Between Depressive Symptoms PRS and Depressive Symptoms at Age 21.90 (n=2380)

PRS Threshold	Beta	95% CIs Low	95% CIs High	*P* value	FDR Adjusted *P* with 0.05 Level	ΔR^2
$5.00x10^{-08}$	0.192	-0.024	0.408	0.082	0.164	0.12%
$5.00\ x10^{-07}$	0.003	-0.220	0.215	0.98	0.994	0.00%
$5.00\ x10^{-06}$	0.088	-0.129	0.305	0.428	0.571	0.02%
$5.00\ x10^{-05}$	0.144	-0.077	0.364	0.202	0.316	0.06%
$5.00\ x10^{-04}$	0.176	-0.041	0.393	0.112	0.207	0.10%
$5.00\ x10^{-03}$	0.371	0.153	0.590	0.0010	0.005	0.46%
$5.00\ x10^{-02}$	0.328	0.109	0.546	0.003	0.013	0.35%
$5.00\ x10^{-01}$	0.352	0.135	0.569	0.001	0.005	0.41%

PRS: Polygenic risk score; FDR: False Discovery rate. Incremental R2 (ΔR2) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models.

Table S10 Association Between Depressive Symptoms PRS and Depressive Symptoms at Age 22.90 (N=2707)

PRS Threshold	Beta	95% CIs Low	95% CIs High	*P* value	FDR Adjusted *P* with 0.05 Level	ΔR^2
$5.00x10^{-08}$	0.067	-0.134	0.268	0.515	0.608	0.01%
$5.00\ x10^{-07}$	0.103	-0.101	0.306	0.321	0.462	0.03%
$5.00\ x10^{-06}$	0.165	-0.039	0.370	0.112	0.212	0.09%
$5.00\ x10^{-05}$	0.150	-0.058	0.358	0.159	0.260	0.07%
$5.00\ x10^{-04}$	0.206	0.003	0.408	0.047	0.103	0.14%
$5.00\ x10^{-03}$	0.427	0.224	0.630	0.0004	0.002	0.61%
$5.00\ x10^{-02}$	0.429	0.227	0.632	0.0003	0.002	0.62%
$5.00\ x10^{-01}$	0.456	0.253	0.658	0.0001	0.001	0.70%

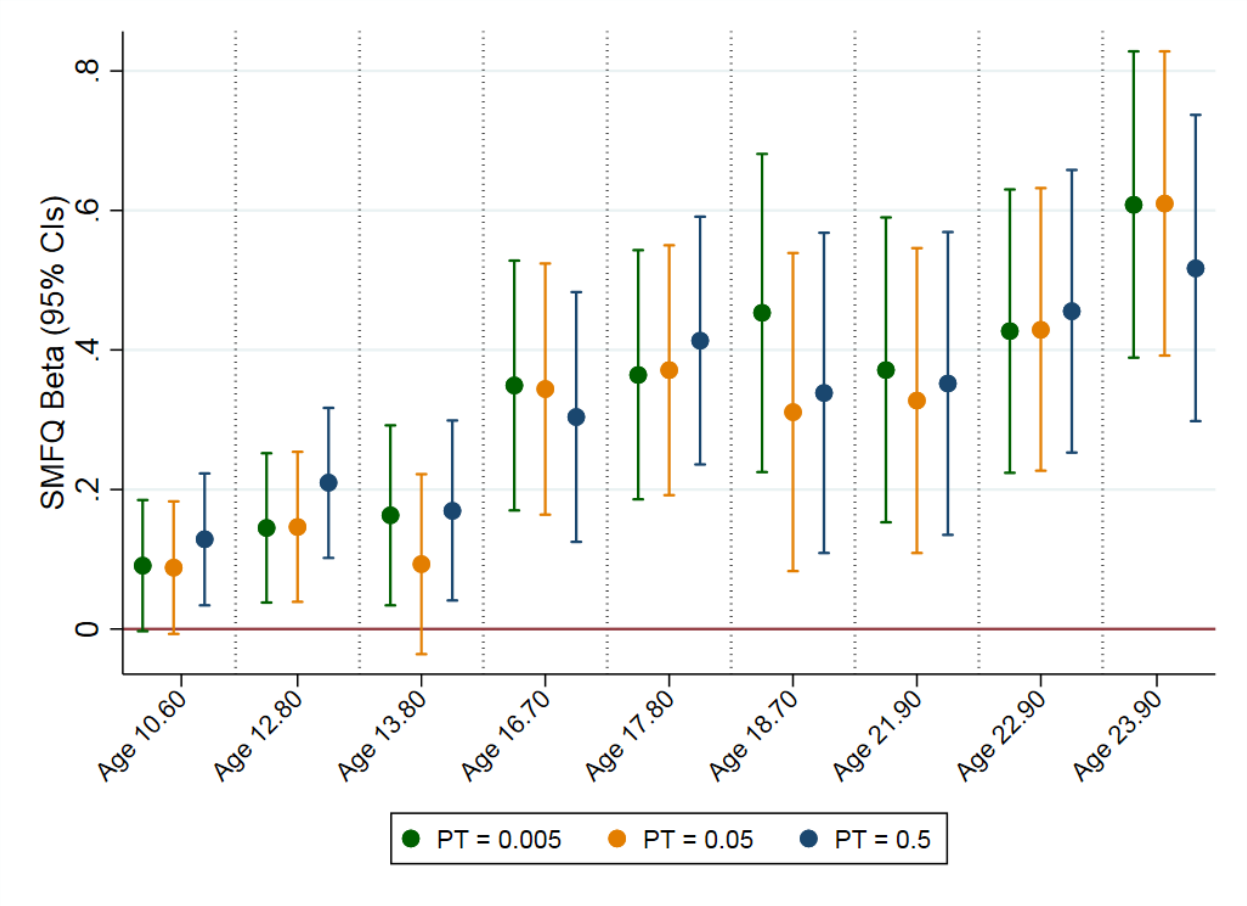
PRS: Polygenic risk score; FDR: False Discovery rate. Incremental R2 (ΔR2) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models.

Table S11 Association Between Depressive Symptoms PRS and Depressive Symptoms at Age 23.90 (N=2715)

PRS Threshold	Beta	95% CIs Low	95% CIs High	*P* value	FDR Adjusted *P* with 0.05 Level	ΔR^2
$5.00x10^{-08}$	0.078	-0.144	0.301	0.49	0.588	0.02%
$5.00\ x10^{-07}$	0.095	-0.125	0.315	0.396	0.548	0.03%
$5.00\ x10^{-06}$	0.206	-0.017	0.428	0.071	0.146	0.12%
$5.00\ x10^{-05}$	0.282	0.056	0.508	0.015	0.037	0.22%
$5.00\ x10^{-04}$	0.276	0.054	0.498	0.015	0.039	0.22%
$5.00\ x10^{-03}$	0.608	0.389	0.828	$5.89x10^{-08}$	$2.12x10^{-06}$	1.07%
$5.00\ x10^{-02}$	0.610	0.392	0.828	$4.64x10^{-08}$	$3.34x10^{-06}$	1.09%
$5.00\ x10^{-01}$	0.517	0.298	0.737	$4.08x10^{-06}$	$9.79x10^{-05}$	0.77%

PRS: Polygenic risk score; FDR: False Discovery rate. Incremental R2 (ΔR2) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models.

Figure S2. Cross-sectional analysis between varying depressive Symptoms PRS (at three thresholds) and depressive symptoms across adolescence



PT: PRS *P* value threshold. SMFQ: Short Mood and Feelings Questionnaire (depressive symptoms). Analysis were adjusted for sex, age and the first ten principal components of ancestry.

Table S12. Association Between Depressive Symptoms PRS and Varying Occasions of Depressive Symptoms

	PRS Threshold								
	0.005 (N_{SNPs} = 5,199)			0.05 (N_{SNPs} = 28,350)			0.5 (N_{SNPs} = 120,422)		
Age	Beta (95% CIs)	FDR *P* Value	ΔR^2 (95% CIs)	Beta (95% CIs)	FDR *P* Value	ΔR^2 (95% CIs)	Beta (95% CIs)	FDR *P* Value	ΔR^2 (95% CIs)
10.67	0.091 (-0.003, 0.185)	0.121	0.07% (0.05%, 0.09%)	0.088 (-0.007, 0.183)	0.223	0.06% (0.03%, 0.09%)	0.129 (0.034, 0.223)	0.026	0.13% (0.07%, 0.19%)
12.81	0.145 (0.038, 0.252)	0.024	0.14% (0.11%, 0.17%)	0.146 (0.039, 0.254)	0.025	0.14% (0.08%, 0.21%)	0.210 (0.102, 0.317)	0.0008	0.29% (0.19%, 0.39%)
13.83	0.163 (0.034, 0.292)	0.035	0.13% (0.08%, 0.18%)	0.093 (-0.036, 0.222)	0.265	0.04% (0.03%, 0.5%)	0.170 (0.041, 0.299)	0.028	0.14% (0.07%, 0.22%)
16.68	0.349 (0.170, 0.528)	0.0009	0.39% (0.35%, 0.43%)	0.344 (0.164, 0.524)	0.001	0.38% (0.30%, 0.45%)	0.304 (0.125, 0.483)	0.005	0.29% (0.25%, 0.35%)
17.82	0.364 (0.186, 0.543)	0.0008	0.48% (0.44%, 0.52%)	0.371 (0.192, 0.550)	0.0007	0.50% (0.40%, 0.61%)	0.413 (0.236, 0.591)	0.00009	0.63% (0.52%, 0.75%)
18.64	0.453 (0.225, 0.681)	0.0007	0.61% (0.47%, 0.76%)	0.311 (0.083, 0.539)	0.024	0.29% (0.21%, 0.38%)	0.339 (0.109, 0.568)	0.015	0.34% (0.22%, 0.46%)
21.95	0.371 (0.153, 0.590)	0.005	0.47% (0.35%, 0.58%)	0.328 (0.109, 0.546)	0.013	0.37% (0.25%, 0.48%)	0.352 (0.135, 0.569)	0.005	0.42% (0.31%, 0.54%)
22.88	0.427 (0.224, 0.630)	0.002	0.61% (0.47%, 0.77%)	0.429 (0.227, 0.632)	0.002	0.63% (0.46%, 0.79%)	0.456 (0.253, 0.658)	0.001	0.70% (0.47%, 0.94%)
23.86	0.608 (0.389, 0.828)	$2.12x10^{-06}$	1.07% (0.76%, 1.37%)	0.610 (0.392, 0.828)	$3.34x10^{-06}$	1.08% (0.81%, 1.36%)	0.517 (0.298, 0.737)	0.0001	0.77% (0.58%, 0.96%)
Average	0.330	-	0.44%	0.302	-	0.38%	0.321	-	0.41%

PRS: Polygenic Risk Score. Upper and lower 95% confidence intervals for the beta are given in (parenthesis). Incremental R2 (ΔR2) or the percentage of variance explained by the polygenic risk score was calculated by first regressing depressive symptoms on age, sex and first ten principal components of ancestry, then including the PRS and comparing the variance explained in the two models. The confidence intervals for ΔR2 were derived using bootstrapping with 1000 repetitions. The average beta and ΔR2 were calculated by taking the average across all occasions.

Table S13. Association Between Depressive Symptoms PRS (threshold = 0.005) and Trajectories of Depressive Symptoms (*N*=6,305)

Parameter	Beta	95% Low CIs	95% High CIs	Std. Err.	*P* Value [b]
Intercept [a]	5.872	5.693	6.051	0.091	< .0001
Age	0.345	0.313	0.377	0.016	< .0001
Age^2	-0.097	-0.107	-0.087	0.005	< .0001
Age^3	-0.005	-0.006	-0.004	0.0004	< .0001
Age^4	0.002	0.002	0.002	0.0001	< .0001
DS PRS [c]	0.319	0.186	0.452	0.068	$2.47x10^{-06}$
DS PRS x Age	0.044	0.012	0.076	0.016	0.007
DS PRS x Age^2	-0.008	-0.018	0.002	0.005	0.108
DS PRS x Age^3	-0.001	-0.001	0.0003	0.0004	0.208
DS PRS x Age^4	0.0002	0.0000	0.0004	0.0001	0.066

PRS: Polygenic Risk Score. DS: Depressive Symptoms. Upper and lower 95% confidence intervals for the beta are given in (parenthesis).
Analysis were adjusted for sex and the first ten principal components of ancestry.
a The intercept was centered to age 16.53, the mean age of all the assessments.
b The *P* values of <.001 represents how that parameter differs from 0.
c The depressive symptoms PRS had a threshold of 0.005 and was standardized to have mean of 0 and a standard deviation of 1.

Table S14. Association Between Depressive Symptoms PRS (threshold = 0.05) and Trajectories of Depressive Symptoms (*N*=6,305)

Parameter	Beta	95% Low CIs	95% High CIs	Std. Err.	*P* Value [b]
Intercept [a]	5.866	5.687	6.045	0.091	< .0001
Age	0.344	0.312	0.376	0.016	< .0001
Age^2	-0.097	-0.107	-0.087	0.005	< .0001
Age^3	-0.005	-0.006	-0.004	0.0004	< .0001
Age^4	0.002	0.002	0.002	0.0001	< .0001
DS PRS [c]	0.363	0.230	0.496	0.068	$8.56x10^{-08}$
DS PRS x Age	0.048	0.016	0.080	0.016	0.003
DS PRS x Age^2	-0.008	-0.018	0.003	0.005	0.143
DS PRS x Age^3	-0.001	-0.001	0.0002	0.0004	0.170
DS PRS x Age^4	0.0001	-0.0001	0.0003	0.0001	0.178

PRS: Polygenic Risk Score. DS: Depressive Symptoms. Upper and lower 95% confidence intervals for the beta are given in (parenthesis).
Analysis were adjusted for sex and the first ten principal components of ancestry.
a The intercept was centered to age 16.53, the mean age of all the assessments.
b The *P* values of <.001 represents how that parameter differs from 0.
c The depressive symptoms PRS had a threshold of 0.05 and was standardized to have mean of 0 and a standard deviation of 1.

Table S15. Association Between Depressive Symptoms PRS (threshold = 0.5) and Trajectories of Depressive Symptoms (*N*=6,305)

Parameter	Beta	95% Low CIs	95% High CIs	Std. Err.	*P* Value [b]
Intercept [a]	5.871	5.692	6.050	0.091	< .0001
Age	0.345	0.313	0.377	0.016	< .0001
Age^2	-0.097	-0.107	-0.087	0.005	< .0001
Age^3	-0.005	-0.006	-0.004	0.0004	< .0001
Age^4	0.002	0.002	0.002	0.0001	< .0001
DS PRS [c]	0.332	0.200	0.465	0.068	$8.52x10^{-07}$
DS PRS x Age	0.036	0.004	0.068	0.016	0.028
DS PRS x Age^2	-0.003	-0.013	0.007	0.005	0.563
DS PRS x Age^3	-0.0003	-0.001	0.001	0.0004	0.481
DS PRS x Age^4	0.0001	-0.0001	0.0003	0.0001	0.520

PRS: Polygenic Risk Score. DS: Depressive Symptoms. Upper and lower 95% confidence intervals for the beta are given in (parenthesis).
Analysis were adjusted for sex and the first ten principal components of ancestry.
a The intercept was centered to age 16.53, the mean age of all the assessments.
b The *P* values of <.001 represents how that parameter differs from 0.
c The depressive symptoms PRS had a threshold of 0.5 and was standardized to have mean of 0 and a standard deviation of 1.

Table S16. Association between the height PRS and trajectories of depressive symptoms (*N*=6,305)

	Beta	**95% Low CIs**	**95% High CIs**	**Std. Err.**	***P*-value**
Intercept	5.863	5.683	6.043	0.092	< .0001
Age	0.343	0.311	0.375	0.016	< .0001
Age^2	-0.097	-0.107	-0.087	0.005	< .0001
Age^3	-0.005	-0.006	-0.004	0.0004	< .0001
Age^4	0.002	0.002	0.002	0.0001	< .0001
HEI PRS	-0.021	-0.154	0.111	0.068	0.753
HEI PRS x Age	0.019	-0.013	0.050	0.016	0.250
HEI PRS x Age^2	0.003	-0.007	0.013	0.005	0.535
HEI PRS x Age^3	-0.0003	-0.001	0.001	0.0004	0.501
HEI PRS x Age^4	-0.0001	-0.0003	0.0001	0.0001	0.400

PRS: Polygenic Risk Score. HEI: Height. Upper and lower 95% confidence intervals for the beta are given in (parenthesis). Analysis were adjusted for sex and the first ten principal components of ancestry.

a The intercept was centered to age 16.53, the mean age of all the assessments.

b The *P* values of <.001 represents how that parameter differs from 0.

c The height PRS had a threshold of 0.5 and was standardized to have mean of 0 and a standard deviation of 1

Figure S3. Association between the height PRS and trajectories of depressive symptoms

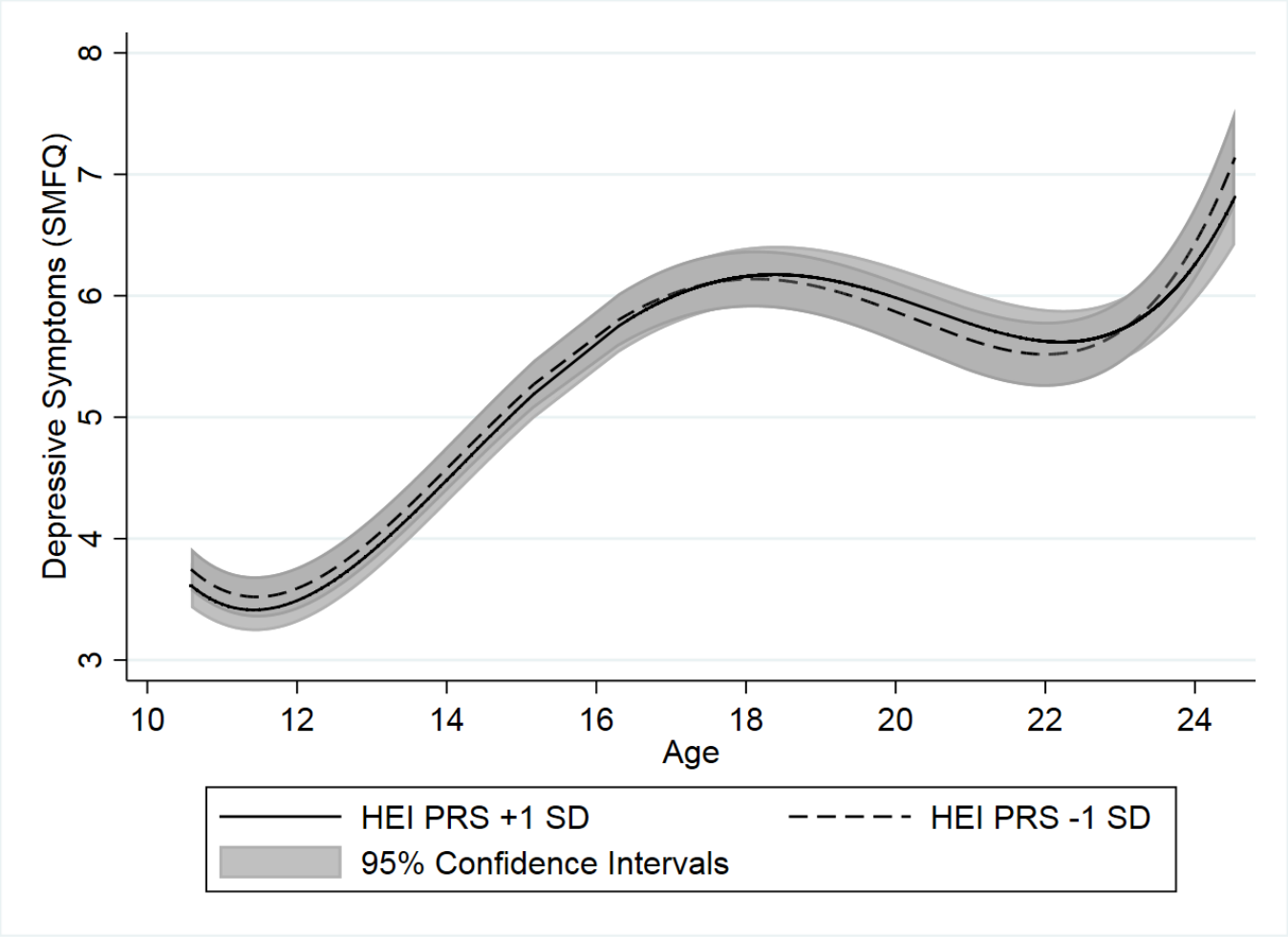


Table S17. Association between the depressive symptoms PRS and trajectories of height (*N*=6,754)

	Beta	**95% Low CIs**	**95% High CIs**	**Std. Err.**	***P*-value**
Intercept	154.031	153.773	154.289	0.132	< .0001
Age	5.209	5.188	5.230	0.011	< .0001
Age^2	-0.237	-0.242	-0.231	0.003	< .0001
DS PRS	-0.085	-0.255	0.086	0.087	0.330
DS PRS x Age	0.007	-0.014	0.028	0.011	0.519
DS PRS x Age^2	-0.001	-0.007	0.004	0.003	0.650

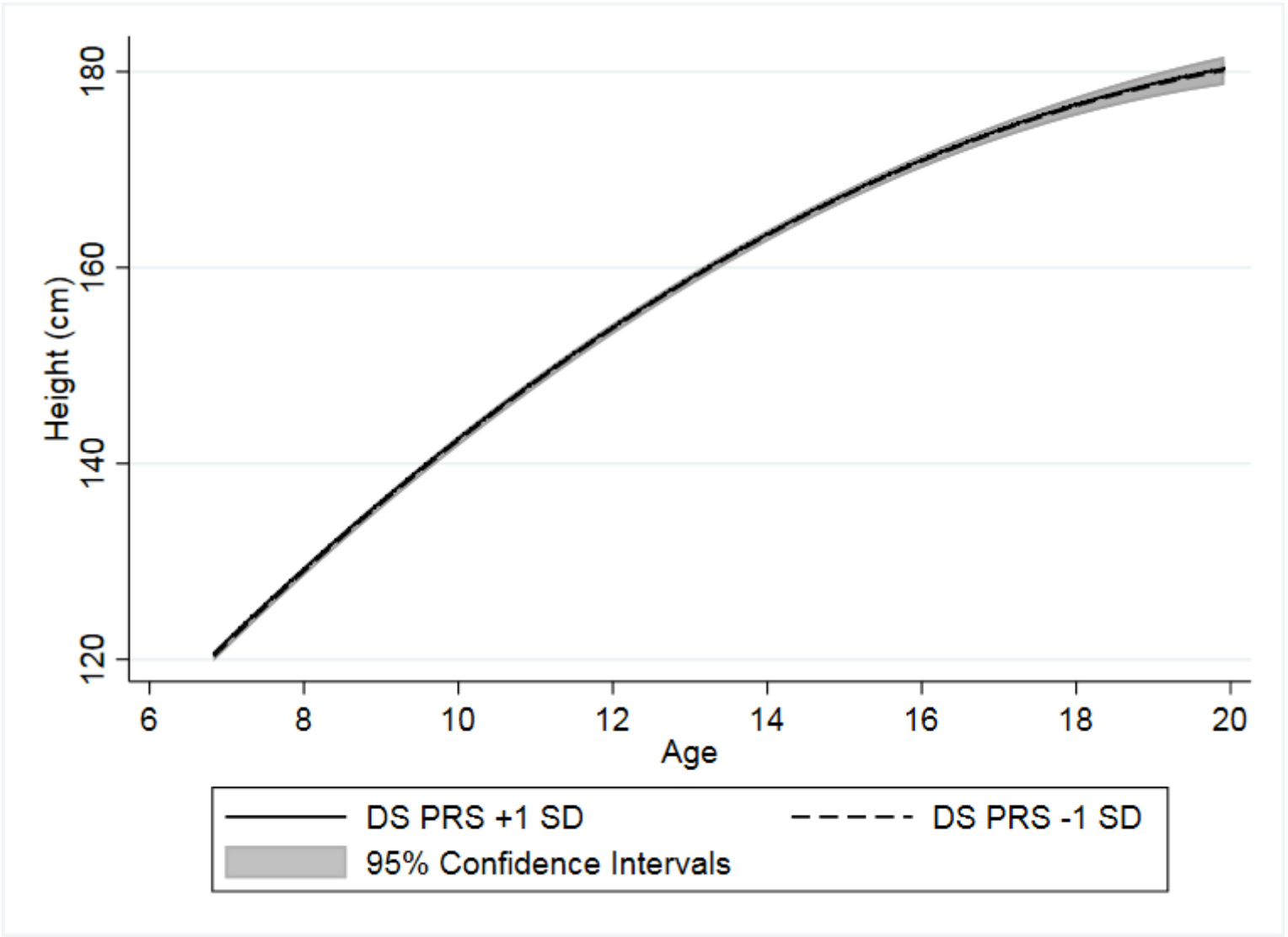
PRS: Polygenic Risk Score. DS: Depressive Symptoms. Upper and lower 95% confidence intervals for the beta are given in (parenthesis). Analysis were adjusted for sex and the first ten principal components of ancestry.

a The intercept was centered to age 12.02, the mean age of all the assessments.

b The *P* values of <.001 represents how that parameter differs from 0.

c The DS PRS had a threshold of 0.5 and was standardized to have mean of 0 and a standard deviation of 1

Figure S4. Association between the depressive symptoms PRS and trajectories of height



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