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Morbidity and use of healthcare services in early childhood

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HEALTH OUTCOMES IN CHILDREN OF PARENTS WITH MENTAL HEALTH CONDITIONS

**MORBIDITY AND USE OF HEALTHCARE
SERVICES IN EARLY CHILDHOOD**

**BY
SIGNE HEUCKENDORFF**

DISSERTATION SUBMITTED 2021



AALBORG UNIVERSITY
DENMARK

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CV



Signe Heuckendorff

I became a medical doctor from University of Copenhagen in 2013. During my studies I had two publications in relation to my bachelor thesis^{1,2*}. I was acquainted with general practice as intern and first year resident in Beder and Silkeborg 2014-2015. Then, I was caught by social medicine and the public health specialty, first as first year resident at Department of Social Medicine & Rehabilitation, Aarhus, 2015-16, and from 2016, as specialist trainee in public health medicine at Aalborg University Hospital at Department of Social Medicine and Child and Adolescent Psychiatry. My special interest is child health and factors influencing child health, which also was the theme of my research training assignment; association between childhood and adolescence overweight and obesity and the impact of maternal education, presented at European Public Health Conference 2018³.

Since 2018, I have been clinical assistant and PhD student at Department of Social Medicine, Aalborg University Hospital. Preliminary results from some of the studies in the thesis have been presented at European Public Health Conference 2019⁴ and World Congress on Public Health 2020^{5,6,7}. Other dissemination activities include supervising three master projects, two medicine and one in public health and teaching medicine students in social medicine.

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1 EXTRAINTestinal MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE: EPIDEMIOLOGY, DIAGNOSIS, AND MANAGEMENT LARSEN* S, BENDTZEN K, NIELSEN OH. *ANN MED*. 2010 MAR;42(2):97-114

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LARSEN* S, BENDTZEN K, NIELSEN OH. *UGESKR LAEGER*. 2009 OCT 19;171(43):3078-83.

3 THE ASSOCIATION BETWEEN CHILDHOOD AND ADOLESCENCE OVERWEIGHT AND OBESITY. HEUCKENDORFF S, LAUSTEN M, FONAGER K. *EUROPEAN JOURNAL OF PUBLIC HEALTH*, VOL. 28, SUPPLEMENT. 4, 2018. DOI: 10.1093/S11428-006-0056-4

4 PARENTAL MENTAL VULNERABILITY AND USE OF HEALTHCARE SERVICES IN INFANTS. HEUCKENDORFF S, JOHANSEN MN, OVERGAARD C, JOHNSEN SP, FONAGER K. *EUROPEAN JOURNAL OF PUBLIC HEALTH*, VOL. 29, SUPPLEMENT 4, 2019. DOI: 10.1093/EURPUB/CKZ187.183

5 2.L. WORKSHOP: POOR PARENTAL MENTAL HEALTH AND IMPACTS ON EARLY CHILD HEALTH IN THE CONTEXT OF DANISH WELFARE STATE. OVERGAARD C, HEUCKENDORFF S. *EUROPEAN JOURNAL OF PUBLIC HEALTH*, VOLUME 30, SUPPLEMENT 5, 2020. DOI: 10.1093/EURPUB/CKAA185.126

6 THE IMPACT OF PARENTAL MENTAL HEALTH AND SOCIOECONOMIC POSITION ON CHILD PRESCHOOL HEALTH. HEUCKENDORFF S, JOHANSEN MN, OVERGAARD C, JOHNSEN SP, FONAGER K. *EUROPEAN JOURNAL OF PUBLIC HEALTH*, VOLUME 30, SUPPLEMENT 5, 2020. DOI: 10.1093/EURPUB/CKAA165.130

7 IMPACT OF MATERNAL MENTAL HEALTH PROBLEMS ON PERINATAL OUTCOMES FOR THE INFANT. CHRISTENSEN LF, HEUCKENDORFF S, FONAGER K, OVERGAARD C. *EUROPEAN JOURNAL OF PUBLIC HEALTH*, VOLUME 30, SUPPLEMENT 5, 2020. DOI: 10.1093/EURPUB/CKAA165.129

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- Peder Kristen Tøfting And Dagmar Tøfting's Foundation (grant number: 64463)

Contributions from these foundations made it possible to conduct this PhD project. However, it should be noted that none of these funding resources had any influence on the study design, data analysis or interpretation of the data in this thesis.

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Signe Heuckendorff, August 2021

ENGLISH SUMMARY

Mental health conditions are common, and the prevalence seems to be increasing. Children of parents with mental health conditions are numerous, and these children are facing higher risks of a range of adverse health outcomes than children of parents without mental health conditions. However, knowledge of the impact of different severities of mental health conditions, such as minor conditions treated solely at primary care, and the impact of the father's mental health is lacking.

This thesis aims to examine the association between parental mental health conditions and early childhood morbidities by comparing children of parents with mental health conditions to children of parents without mental health conditions regarding: 1) risks of adverse perinatal outcomes, 2) use of healthcare services during the first year of life, 3) risks of asthma at preschool age and 4) risks of functional gastrointestinal disorders at school age. Secondary aims are to examine a) whether parental mental health conditions and disadvantaged socioeconomic position interacted on the risk of asthma and b) the association between attendance compared to no attendance in the preventive child health examination in general practice and functional gastrointestinal disorder in the overall population and within strata of mental health conditions

Four nationwide, register-based studies were performed including all children in Denmark born 2000-2016. Exposure was parental mental health condition categorised based on the level on mental health care into minor conditions treated solely at primary care, moderate and severe conditions requiring specialised psychiatric care with the most severe conditions as a separate category.

For all four studies, a gradient of socioeconomic disadvantaged conditions was seen (higher shares of parents with lower educational level and single parents) with increasing severity of mental health condition. Compared to children of parents without mental health conditions, children of parents with mental health conditions had higher risks of adverse perinatal outcomes, more healthcare contacts and higher risks of asthma and functional gastrointestinal disorder. The associations were evident for both minor, moderate and severe mental health conditions and strongest for maternal exposure. Double exposure of maternal mental health condition and disadvantaged socioeconomic position was associated with an extra high risk of asthma. Preventive child health examination attendance in general practice compared to no attendance was associated with higher risk of functional gastrointestinal disorder, both in the overall population and within strata of parental mental health conditions.

The findings of this thesis emphasised the importance of focusing on both parents' mental health including conditions treated solely at primary care. Further, more focus on the presence of other risk factors such as parental mental health conditions and

socioeconomic disadvantaged conditions are warranted. Identifying the children at risk followed by action is key. Improved collaboration and communication within the healthcare system as well as between different sectors, e.g. health and social sector, should be considered. Further research is needed to investigate the causal mechanisms underlying the presented findings.

DANSK RESUME

Mentale helbredsproblemer er hyppige, og prævalensen ser ud til at være stigende. Børn af forældre med mentale helbredsproblemer er talrige, og disse børn har en højere risiko for en lang række negative helbredsudfald sammenlignet med børn af forældre uden mentale helbredsproblemer. Dog mangler viden om betydningen af forskellige sværhedsgrader af mentale helbredsproblemer såsom lettere/mindre komplekse helbredsproblemer behandlet udelukkende i primærsektoren samt betydningen af fars mentale helbred.

Formålet med denne afhandling er at undersøge sammenhængen mellem forældrenes mentale helbredsproblemer og helbredsudfald i tidlig barndom ved at sammenligne børn af forældre med mentale helbredsproblemer med børn af forældre uden vedrørende: 1) risiko for negative perinatale udfald, 2) brug af sundhedsydelser i løbet af det første leveår, 3) risiko for astma i førskolealderen, og 4) risiko for funktionel mavetarmlidelse. Sekundære formål er undersøge a) om forældrenes mentale helbredsproblemer og dårligt stillet socioøkonomisk position interagerer på risikoen for astma og b) associationen mellem deltagelse sammenlignet med ikke-deltagelse i forebyggende børneundersøgelser i almen praksis og funktionelle mavetarmlidelse i den overordnede population samt i strata af mentale helbredsproblemer.

Fire landsdækkende, registerbaserede studier blev udført inkluderende alle børn i Danmark født fra 2000-2016. Eksponering var forældrenes mentale helbredsproblemer baseret på behandlingsniveau i lettere mentale helbredsproblemer behandlet udelukkende i primærsektoren samt moderate og svære helbredsproblemer behandlet i psykiatrisk regi med de sværeste lidelser i en separat kategori.

I alle fire studier sås højere andele af forældre med kort uddannelse og enlige forældre med stigende sværhedsgrad af mentale helbredsproblemer. Sammenlignet med børn af forældre uden mentale helbredsproblemer havde børn af forældre med mentale helbredsproblemer højere risiko for negative perinatale udfald, flere kontakter til sundhedsvæsenet og højere risiko for astma og funktionel mavetarmlidelse. Associationen var evident for både lettere, moderate og svære mentale helbredsproblemer og stærkest for mors eksponering. Dobbelteksponering for mors mentale helbredsproblemer og dårligt stillet socioøkonomisk position var associeret med en ekstrahøj risiko for astma. Deltagelse i forebyggende børneundersøgelser sammenlignet med ikke-deltagelse var associeret med en højere risiko for funktionel mavetarmlidelse både i den overordnede population samt i strata af forældrenes mentale helbredsproblemer.

Fundene i denne afhandling fremhæver vigtigheden af at fokusere på forældrenes generelle mentale helbred inklusive tilstande udelukkende behandlet i primærsektoren. Desuden er der et behov for et øget fokus på tilstedeværelsen af flere

risikofaktorer som mentale helbredsproblemer hos forældrene samt dårligt stillede socioøkonomiske betingelser. Identifikation af børn i risiko efterfulgt af handling er vigtigt. Forbedret samarbejde og kommunikation indenfor sundhedsvæsenet samt mellem forskellige sektorer, f.eks. sundhedssektoren og socialektoren, kan måske bedre udfaldene for børn af forældre med mentale helbredsproblemer, men der er behov for flere undersøgelser til at undersøge de bagvedliggende mekanismer nærmere.

ARTICLES OF THE THESIS

STUDY I

Heuckendorff S, Christensen LF, Fonager K, Overgaard C. Risk of adverse perinatal outcomes in infants born to mothers with mental health conditions. Manuscript published in *Acta Obstetrica et Gynecologica Scandinavica* 2021, doi:10.1111/aogs.14241

STUDY II

Heuckendorff S, Johansen MN, Johnsen SP, Overgaard C, Fonager K. Parental mental health conditions and use of healthcare services in children the first year of life– a register-based, nationwide study. Manuscript published in *BMC Public Health* 2021; 21:557

STUDY III

Heuckendorff S, Johansen MN, Overgaard C, Johnsen SP, Kelly Y, Fonager K. Parental mental health, socioeconomic position and the risk of asthma in children– a nationwide Danish register study. Manuscript under peer-review. *European Journal of Public Health*

STUDY IV

Heuckendorff S, Johansen MN, Overgaard C, Johnsen SP, Thomsen JL, Fonager K. Parental mental health and preventive child health examination participation are associated with functional gastrointestinal disorder in children. Manuscript in preparation.

ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical Classification System
CI	confidence interval
CPR	personal identification number
FGID	functional gastrointestinal disorder
GP	general practitioner
ICD-10	International Classification of Diseases, 10 th revision
IR	incidence rate
IRR	incidence rate ratio
ISCED	International Standard Classification of Education
OR	odds ratio
PCHE	preventive child health examination
PTSD	posttraumatic stress disorder
RERI	relative excess risk of interaction
RR	risk ratio
SEP	socioeconomic position
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor

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CHAPTER 1. INTRODUCTION

The health of children is affected by their surrounding environment, by the ‘conditions in which they are born, grow up and live’ – also known as the social determinants of health¹. The unequal distribution of these determinants leads to inequalities in health, and inequalities in child health are often described in relation to their parent’s socioeconomic conditions. The most recent status from the Danish Health Authority reported graded relationships between maternal education and a range of adverse child health outcomes, including still births, neonatal deaths, <5-years mortality, preterm birth, small for gestational age, breast-feeding and dental health, as well as between parental social group and overweight/obesity at age 11-15².

Child and parental health are closely related, and another important determinant influencing child health, however less well-described, is the mental health of the parents. Children of parents with mental health conditions are at risk of a wide range of health disadvantages such as preterm birth and small for gestational age³⁻⁶, injuries, asthma and overweight⁷, a range of less specified morbidities^{8,9}, behavioural and emotional problems¹⁰ and mental disorders^{9,11,12}. These children (should) represent a public health priority¹³:

1.1. CHILD HEALTH AS A DETERMINANT OF HEALTH OVER A LIFE COURSE

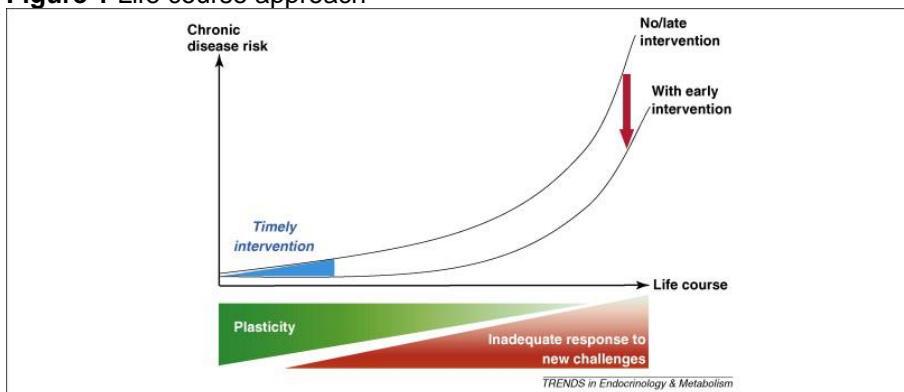
Why focus on child health? First and foremost, inequalities in childhood are per se unfair and child health should be a public health priority. Children who experience good health in childhood are far more likely to have good health as adults. The early development of the child, including health, physical, social-emotional and language/cognitive development, strongly influences basic learning, school success, economic participation, social citizenry, and future health¹⁴. Hence, childhood morbidity and child health disparities tend to persist into adult life¹⁵.

Early intervention is therefore crucial. Moreover, economic studies report early interventions have high benefit-costs ratios and rates of return, and more specifically that the earlier the investment is made, the greater the return on investment and future cost savings from prevention and early intervention¹⁶. Thus, early childhood has been referred to as the critical time window of intervention¹⁵.

A life course approach highlights an awareness that health-protective and health-damaging influences may be more or less important at particular times in life, and these influences have effects that accumulate and interact over time¹⁵. Figure 1 illustrates that the trajectory of adult disease risk is set already in early life¹⁷. The risk of chronic disease increases throughout the life course as a result of declining

plasticity (green triangle) and the result of cumulative effects if inadequate responses to new challenges (red triangle)¹⁷. Timely interventions in early life (blue area) can have a large effect on disease risk later (red arrow)¹⁷.

Figure 1 Life course approach



Reprinted from Trends in Endocrinol Metab, vol. 21(4), Godfrey KM, Gluckman PD, Hanson MA, Developmental origins of metabolic disease: life course and intergenerational perspectives, Pages 199-205, Copyright (2010), with permission from Elsevier

1.2. THE MAGNITUDE OF MENTAL HEALTH CONDITIONS

The overall prevalence of self-reported poor mental health in Denmark has increased from 10% in 2010 to 13.2% in 2017 (OR 1.40 (95% CI 1.36-1.43) adjusted for sex and age)¹⁸. The highest prevalence of poor mental health was seen in the childbearing age; between 16.3-23.8% in women aged 16-44 years and for men in the same age groups between 12.2-13.9%¹⁸.

Thus, children of parents with mental health conditions represent a large and possibly growing population; a Swedish study using information on diagnoses from in- and outpatient care reported an overall prevalence of 9.53% (95% CI 9.50-9.57) children with parents with diagnosed mental illness¹⁹. Using primary care data, a UK study reported an overall prevalence of maternal mental illness of 23.2% (95% CI 23.1-23.4)²⁰. Still, the prevalence of children in Denmark of parents with mental health conditions are needed. However, a very recent Danish study including information from both primary and secondary care found an overall prevalence of 39.1% (95% CI 39.0-39.2) of all children aged 0-16 years with at least one parent with a mental health condition²¹. Further, the prevalence of children with at least one parent with a psychiatric diagnosis from secondary care was 12.8% (95% CI 12.7-12.8)²¹.

Mental health conditions are related to increased risk of somatic morbidity, premature death, increased use of health care services, sickness absence and additional number of disability pension²². Symptoms such as sad mood, loss of interest, fatigue, low energy, cognitive impairment, changes in appetite, motor activity or sleep patterns may be symptoms of several mental disorders. Moreover, in parents mental health conditions may affect parenting; for example some developmental phases in the child's life may be difficult dealing with and some diagnoses may interact the child's temperament and characteristics^{23–25}.

To summarise; even in the context of the Danish welfare state, inequalities in child health exists^{2,8,9}. The trajectory of adult health is set during childhood, and early intervention is crucial. The prevalence of adults with mental health conditions increases and a substantial proportion of the children in Denmark have parent(s) with mental health conditions. There is a need for more knowledge of the health risks of these children, which will be further explained and elaborated in the following sections.

1.3. SOCIAL DETERMINANTS OF CHILD HEALTH

Parental mental health is considered as a social determinant of child health²⁶. As other social determinants of health, mental health conditions are socially distributed such that increased rates of mental health conditions systematically are associated with disadvantaged socioeconomic conditions^{19,27}. The social determinants of child health, including parental mental health, are closely related and the pathways, through which the social determinants affect child health, might be similar²⁶. The mechanisms are several and may include material, psychosocial, behavioural and structural pathways as described by Pearce and colleagues²⁶. These are briefly summarised below.

The material pathway refers to material living conditions and the fact that those from more advantaged social positions have greater access to the resources that support health, such as a warm safe home and nutritional foods²⁶.

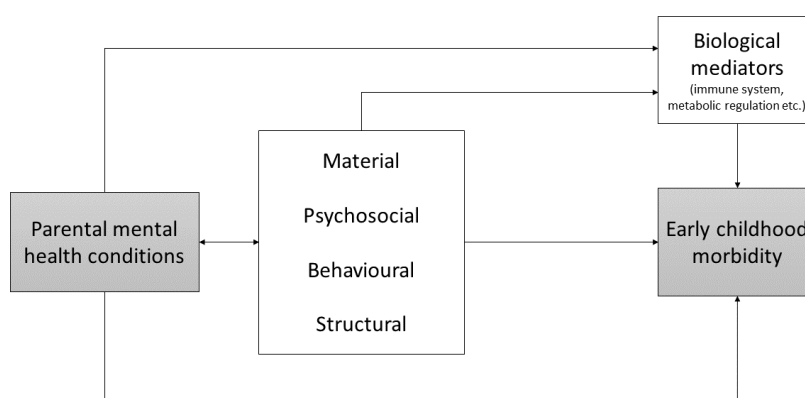
The psychosocial pathway focusses on the stressor produced by living in social disadvantage and their influence on health and health behaviours and further on the feelings of inferiority, subordination or lack of control that may be produced by social inequality, in turn influencing physical and mental well-being via neuroendocrine pathways²⁶.

The behavioural pathway suggests that health behaviours, such as smoking, diet and physical activity being more prevalent in less advantaged groups, lead to health inequalities. These health behaviours certainly influence health; however, this pathway might be less important than others²⁶. Further, this pathway has been criticised for a too simplistic focus as health behaviours are heavily influenced by the

other pathways and social determinants of health²⁶; every parent wants the best for their child including the child's health, but their capacity to do so may be influenced by other pathways and by the structural determinant of child health²⁶.

Finally, socioeconomic, political, cultural and commercial structures influence the control, distribution and accessibility of power, resources and services across the population and refers to a structural pathway²⁶. It has been claimed that these structural determinants may be the root causes of health inequalities²⁶.

Figure 2 Pathways from parental mental health conditions to adverse child health outcomes



1.4. PARENTAL MENTAL HEALTH AS A DETERMINANT OF CHILD HEALTH

The mechanisms underlying the association between parental mental health conditions and child health outcomes are highly complex and possibly include several pathways as depicted in Figure 2^{26,28}. Pathways to child health including parental mental health and the interplay between parental mental health and other important social determinants of child health will be elaborated in the following.

Child health may be affected directly through shared genetics or by in utero exposure to e.g. medication. Several other determinants of child health also affect parental mental health conditions and vice versa. For example, socioeconomic disadvantage and mental health might have a mutual negative effect/bi-directional relationship, such as experience of financial strain can have a negative impact on mental health, which in turn makes it harder to keep a job. Further, mental health conditions during early adulthood may affect the capacity to complete an education and consequently

leading to lower payed occupation and poor jobs, which might lead to material hardship and poor housing quality.

Cooper and Steward has argued that the mechanism through which e.g. poverty affects child's outcomes to a larger extent is explained by parental stress, depression, relationship conflicts and parenting behaviours rather than by a material mechanism e.g. investments in goods and services²⁹.

Some aspects of parenting may fit in the psychosocial pathway. Negative maternal behaviour, such as negative expressions or anger, was associated with depression²⁵, and negative parental behaviour might contribute to increased stress in the child and affecting child health through the mechanism of toxic stress response as described below. A review examining studies that isolated the effects of the environment from genetic and prenatal influences found evidence indicating that maternal depression was associated with child outcomes through environmental pathways²⁸. Further, stigmatisation and fear in relation to be a parent with a mental health condition³⁰ may also act through this mechanism.

Other examples of factors within the psychosocial pathway might include the stressors relating to lack of social support³¹. This may be of special importance in relation to mental health as lack of social support and not living with a partner were reported associated with worse mental health³². Furthermore, supportive relationships and social networks might be important buffers between parental mental health condition and adverse child health³³.

Behavioural mechanisms between mental health conditions of the parents and adverse child health include smoking among others as people with poor mental health are more likely to smoke than people without¹⁸. People with mental illness need another and more support to quit smoking than the general population³⁴ and parental smoking might be an important mediator between parental mental health and child health. Further, mental health conditions may affect parenting²⁵, e.g. depression was found associated with a range of difficulties in their parenting behaviour²⁵, and some aspects of parenting might fit in the behavioural pathway. For example, interactions during meals and screen time rules can have an impact on childhood overweight²⁶.

A Danish study reported more difficulties in understanding health information and being able to actively engage with healthcare providers in people with mental health conditions compared to the general population³⁵. This may also apply for parents with mental health conditions. Parental mental health conditions might interfere with the parent's capacity to handle their children's symptoms in relation to available health information and further to communicate their children's needs to healthcare professionals.

Structural factors may influence the impact of parental mental health on child health. Examples of these factors include access to mental health care and policies on sickness absence and benefits. Although the Danish healthcare system in general are characterised by free access, there is co-payment of therapy at psychologists after referral from the general practitioner and full self-payment without a referral³⁶ making it difficult for people with less financial resources to afford treatment.

Parental mental health conditions may affect child health through a toxic stress response resulting from a strong, frequent or prolonged activation of the body's stress response systems in the absence of the buffering protection of a supportive, adult relationship³³. This might lead to physiological disruptions in the development of the body's response system and affect the developing brain, immune, cardiovascular, and metabolic systems, resulting in long-lasting effects on health³³. Moreover, several stressors arising from the psychosocial pathway might affect child health through similar mechanisms.

A gradient of child health inequalities?

A gradient exists concerning health inequalities meaning that an increasing risk of morbidity and mortality is seen with decreasing level of e.g. education or income. Whether a gradient regarding the severity of mental health conditions exist, such that also minor mental health conditions are associated with an increased risk of poor child health and severe mental illness is associated with an even larger risk, is unknown. However, studies indicated that mental illness severity rather than the diagnosis is related to parenting competence and outcomes in the children^{23,37,38} and another study reported increasing risk of preterm birth with increasing severity of depression³⁹.

1.5. CURRENT KNOWLEDGE AND KNOWLEDGE GAPS

Parental mental health conditions are associated with a range of adverse health outcomes of the child^{7,11,40}. Further, parental mental health conditions or mental illness of a household member are often referred to as an adverse childhood experience, which is associated with increased risk of morbidity and premature mortality^{41–43}.

It is well-described that parental mental health conditions are associated with an increased risk of a range of child outcomes such as mental disorders^{9,11,37,44,45}. Increased risk of physical morbidity, e.g. asthma, other atopic diseases, accidents/injuries and overweight/obesity in children is also reported mainly for maternal depression⁷ as well as broadly defined childhood morbidities and parental severe mental illness^{8,9}, but the information is little¹³. More specific knowledge gaps are elaborated in the following subsections.

Overall, existing knowledge mainly focus on the impact of maternal depression⁷ and severe mental illness^{8,9}. However, as mentioned in section 1.4., it is unknown whether different severities of poor parental mental health yield different impacts on child health. Thus, a broader approach to different severities of mental health is missing.

1.5.1. PERINATAL OUTCOMES

The impact of poor parental mental health is seen from the very beginning of the child's life. Several mental disorders in the mother has been found associated with adverse perinatal outcomes. For example was maternal schizophrenia⁴⁶, bipolar disorder³, borderline personality disorder⁴⁷, PTSD (posttraumatic stress disorder)⁴⁸ and intellectual disability⁴⁹ associated with several adverse perinatal outcomes such as preterm birth^{3,46-49}, small for gestational age among others^{3,46}. Also less severe mental illness (anxiety^{5,50}, depression^{4,6,51,52}) increased the risk of preterm birth^{4-6,50-52} and low birth weight^{4-6,50,51}.

However, most information exists on preterm birth and low birthweight and less on other adverse perinatal outcomes such as respiratory distress syndrome, neonatal seizures, low Apgar scores⁵³, neonatal abstinence syndrome or sepsis (all of the mentioned outcomes^{3,46}). High-quality prospective cohort studies designed to assess the association between maternal prenatal mental health conditions and adverse perinatal outcomes including neonatal mortality are needed⁵⁴. Further, knowledge of the impact of different severities of mental health conditions as well as the impact of the mental health of the father is lacking.

1.5.2. HEALTHCARE UTILISATION

Along with the other mentioned health consequences in children of parents with mental health conditions are increased use of healthcare services.

The first year of life, morbidity in children is primarily characterised by infections and especially upper airway infections account for a large share of the healthcare contacts to both general practices and hospitals⁵⁵. A great part of the morbidity the first year of life is handled by the general practitioner (GP) but diagnoses from the primary healthcare are not available in the registers. Another way to measure morbidity is by measuring the use to healthcare services. Further, strengthening and broadening the understanding of the association between parental mental health conditions and children's healthcare utilisation help policymakers to understand more about the hidden costs of parental mental health conditions and facilitate prioritising and planning of services and interventions.

Existing knowledge on the healthcare utilisation in early life in children of parents with poor mental health primarily focus on maternal depression⁵⁶⁻⁶⁰ or are limited by

cross-sectional design exposing the possibility of reverse causality bias^{57,59,61–64}. Other studies included self-reported symptoms^{58,61} with limitations of recall bias. Overall, all studies reported more healthcare contacts in children of mothers with depression compared to children without^{56–62}. Although mental health conditions such as depression include a wide range of symptoms, severities, and thus disabilities, existing literature does not distinguish between different severities or complexities of studied conditions. Consequently, the impact of different degrees of parental mental health conditions is unknown. Thus, there is a lack of prospective cohort studies exploring the impact of different severities of mental health conditions on the use of healthcare services in children.

1.5.3. COMMON CHILDHOOD MORBIDITIES

One of the major childhood morbidities is asthma that affects 5-10% of children⁶⁵. Previous studies report that maternal depression or anxiety was associated with increased risk of asthma^{66,67}. However, the literature is primarily limited to children of mothers with depression or anxiety^{7,68}. One study reported a small association between paternal depression or anxiety and childhood asthma interpreted as residual confounding⁶⁷, but besides this, the evidence of the impact of father's mental health is sparse⁷.

Another common condition in childhood is functional gastrointestinal disorders affecting more than one in ten children^{69–71}. Functional gastrointestinal disorders are defined by the Rome IV criteria⁷⁰ and consists of functional nausea and vomiting disorders, functional abdominal pain disorders (including functional dyspepsia and irritable bowel syndrome) and functional defecation disorders (such as functional constipation)⁷⁰. Overall, the literature of the impact of poor parental mental health is limited to parental anxiety⁷² and maternal depression⁷³; however these studies examine recurrent abdominal pain and health complains including stomach ache and not specifically on functional gastrointestinal disorder. Thus, the knowledge in this field is sparse.

Double trouble – double risk?

The relationship between mental health and socioeconomic position is bi-directional: Poor mental health may lead to reduced income and employment, which lead to poverty/material hardship and in turn increases the risk of poor mental health²⁷. Moreover, people in socioeconomic disadvantage suffer disproportionately from poor mental health and the consequence hereof²⁷. Further, as described in section 1.3. socioeconomic position and parental mental health are social determinants of child health. These three points may rise the question: Does children of parents with the combination of poor mental health and socioeconomic disadvantage have an even higher risk of morbidity than children only exposed to one or the other factor? To the best of our knowledge, no prior studies have examined whether these factors interact

to describe a potential excess risk for children of parents with the combination of poor mental health and disadvantaged socioeconomic position.

Preventive child health examinations in general practice

Preventive child health examinations by general practitioners (GPs) are in Denmark on a routine basis offered to children aged 0-5 in Denmark to give the child the best conditions for a healthy development (physical, mental and social)⁷⁴. Further, and according to the guideline from the Danish Health Authority⁷⁴, the GP has a central role in the early discovery of children and families with special needs.

PCHE has earlier been suggested as an intervention to reduce inequality in child health⁷⁵, and efforts have been made to get knowledge of who is not participating⁷⁶⁻⁷⁸; however, the knowledge of the potential effect of preventive child health examinations is absent⁷⁹. An evaluation of the preventive child health examinations from 2007⁷⁸ reported that the GPs made findings in one out seven examinations but do report on the impact of the finding. A recent report on interventions against inequalities in health from the Danish Health Authority⁸⁰ based on a systematic review do not mention the preventive child health examinations at GP at all, and it is noticed that the use of healthcare services in Denmark is poorly examined⁸⁰. However, the report emphasised that “there is no evidence that the used methods are not effective” and conclude that an increased focus on outreach work and retained efforts for families with short education and social vulnerability are needed to reduce inequalities in health for children⁸⁰.

Thus, it is hypothesised that preventive child health examination participation might reduce inequality in child health as children of parents with poor mental health might in particular benefit from the preventive child health examinations through early detection, prevention and counselling from the GP with knowledge about both parents and child. But evidence is lacking.

Functional gastrointestinal disorders are preferably treated at GP^{81,82}. It is hypothesised that preventive child health examination participation compared to not participation is associated with a lower risk of a hospital diagnosis of function gastrointestinal disorder in children in the overall population and especially in children of parents with mental health conditions.

1.5.4. WHAT ABOUT THE FATHER?

In Denmark and many other countries, the fathers have a central role in the family, not only the mother. Fathers today are more involved in their children's life than earlier, and compared to other countries, fathers in Denmark belong to the group spending most time with their children^{83,84}. Further, fathers' parenting stress affect children's cognitive and language outcomes⁸⁵. Fathers can, like mothers, be affected by poor mental health. A recent Swedish study including hospital diagnoses of mental

illness found that the prevalence of children exposure to maternal mental illness (5.91% (95% CI 5.89-5.94)) was approximately one third higher than exposure to paternal mental illness (4.28% (95% CI 4.26-4.31))¹⁹. A Danish study found a prevalence of 18% (95% CI 18.3-18.5) of all children exposed to paternal mental health conditions. Of these were 11.3% (95% CI 11.2-11.4) minor conditions and 6.1% (95% CI 6.1-6.1) and 1.0 (95% 1.0-1.0) moderate and severe, respectively²¹.

However, the father is absent in the majority of the literature of the impact of parental mental health on child health¹³, which was also noted by the authors of a systematic review and meta-analysis from 2019⁷. Although the data might be available, the influence of the mental health of the father is often not investigated^{7,13,56,58,68,73}. Further, the limited literature most focus on paternal depression and emotional and behavioural outcomes in the child^{28,86}.

1.5.5. RATIONALE FOR THIS RESEARCH

As outlined in the previous sections, poor mental health of the parent, especially the mother, is associated with several child morbidities in early childhood, but the existing literature do not differentiate the severity/complexity of the mental health conditions of the parents. Mental health conditions, such as depression, include a wide range of symptoms, severities and thus disabilities that might have different effects on child health. Existing literature primarily focus on depression^{7,56,73} and severe mental illness^{8,9} and often using health data from only secondary care settings and medication^{8,9,67,73} with no information from primary care where the least severe mental health conditions are treated. Further, existing studies have not investigated the impact of the father's mental health⁷.

There is a need for studies exploring how minor mental health conditions treated solely in primary care as well as more severe mental health conditions requiring specialised care – of both mother and father – is associated with early childhood morbidities.

This present thesis presents an opportunity to explore this field in a setting of an entire nation and a very large population.

CHAPTER 2. AIMS OF THE THESIS

2.1. OVERALL OBJECTIVE

The overall objective of this thesis was to contribute with new knowledge of the impact of different severities of mental health conditions of the mother and the father on early childhood morbidities and use of healthcare services for decisionmakers and health professionals to prioritise resources and plan interventions.

In order to do so, following aims were outlined:

2.2. AIM I

To examine the association between maternal mental health status and perinatal health outcomes in the infant (study I).

2.3. AIM II

To examine the associations between different combinations maternal and paternal mental health conditions and the child's use of healthcare services the first year of life (study II).

2.4. AIM III

To examine the associations between maternal and paternal mental health conditions and child preschool asthma and further, to examine whether parental mental health conditions interacted with disadvantaged socioeconomic position (study III).

2.5. AIM IV

To examine, first, the association between parental mental health conditions and a hospital diagnosis of functional gastrointestinal disorder in children at the age of six, secondly, to examine the association between preventive child health examination participation and a hospital diagnosis of functional gastrointestinal disorder in the overall population and within strata of parental mental health conditions (study IV).

CHAPTER 3. METHODS

This chapter describes the methods of the four studies that this thesis was based on. To reduce repetition of the information in the articles, some details have been left out of the thesis. Thus, details not presented here, may be in the specific article.

The four studies were all designed as cohort studies based on the Danish nationwide registers. Table 1 gives a brief overview of studies' methods.

Table 1 Overview of the methods of the four studies

Study	I	II	III	IV
Population	All children born from 2000 to 2016 N=1,021,126	All children born between 2000-2016 N=964,395	All children born from 2000 to 2014 N=925,288	All children born from 2000 to 2011 N=750,379
Exposure	Maternal mental health 12 months prior childbirth	Parental mental health (mother and father combined) five years prior childbirth	Parental mental health (mother and father separate) five years prior baseline at age three Socioeconomic position	Parental mental health (mother and father separate) five years prior baseline at age six Attendance at preventive child health examinations
Outcome	Perinatal outcomes (first 28 days of life)	Use of healthcare services the first year of life	Asthma from age three to five	Functional gastrointestinal disorder from age six to seven
Method of analysis	Modified Poisson regression	Negative binomial regression	Negative binomial regression	Negative binomial regression

3.1. SETTINGS

The Danish healthcare system is primarily financed through taxes, covering 84% of the total healthcare expenditure⁸⁷. Out-of-pocket co-payments are e.g. through contributions to costs of medications⁸⁷ and therapy at psychologists after referral from GP (60% co-payment)³⁶. Private hospitals only account for a small amount of the healthcare in Denmark (less than 1% of hospital beds)⁸⁷ and emergency departments are only located at public hospitals.

GPs are the first point of contact for patients, except for emergencies, and thus has a key position as gatekeepers to the secondary (specialized) care, including referrals to office-based/private practising specialists and inpatient and outpatient hospital care⁸⁷. GPs are available during regular daytime hours. In case of illness outside of normal openings hours, an out-of-hour medical service is available covered via a rotation system among GPs in a given geographical area. One exception is the Capital Region, which, since 2014, has had its own coverage system⁸⁷.

The CPR number, an abbreviation of ‘Central Person Register’, was introduced in 1968 and is a unique personal identification number assigned to all Danish citizens⁸⁸. All national, public registers use the CPR number, which allows for individual level linkage between the registers⁸⁸.

3.2. DATA SOURCES

This thesis was based on data from following health registers:

3.2.1. THE DANISH NATIONAL PATIENT REGISTER

The Danish National Patient Register was established in 1977 and reached complete nationwide coverage in 1978⁸⁹. All data on psychiatric inpatient and outpatient contacts from the Danish Psychiatric Central Research Register has been an integrated part of Danish National Patient Register since 1995⁹⁰. Data in the Danish National Patient Register are updated continuously with information on administrative data, diagnoses, treatments and examinations. The diagnoses are based on International Classification of Diseases, 10th revision (ICD-10) since 1994⁸⁹. The primary diagnosis being the main reason for the hospital contact is registered, and, when relevant, secondary diagnoses supplement by identifying other relevant diseases related to the current hospital contact such as chronic diseases⁸⁹.

3.2.2. THE DANISH NATIONAL PRESCRIPTION REGISTER

The Danish National Prescription Register holds information on redeemed prescriptions including the Anatomical Therapeutic Chemical (ATC) code of the drug and dispensing date. The Danish National Prescription Register does not have data on over-the-counter drugs⁹¹.

3.2.3. THE DANISH NATIONAL HEALTH SERVICE REGISTER FOR PRIMARY HEALTHCARE

The Danish National Health Service Register for Primary Healthcare holds information about activities of health professionals, such as GPs, practising medical specialists and psychologists, contracted with the tax-funded public healthcare system⁹².

3.2.4. THE DANISH MEDICAL BIRTH REGISTER

The Danish Medical Birth Register was established in 1973 and contains primarily data from the Danish National Patient Register supplemented with parity and maternal smoking during pregnancy among others⁹³.

3.2.5. OTHER REGISTERS

Further, data from following registers were used:

- The Population Education Register holds information on individuals' highest completed education⁹⁴. The education codes from this registers transforms easily into the International Standard Classification of Education (ISCED) codes^{94,95}.
- The Income Statistics Register⁹⁶ contains information on public transfer payments, capital income and socioeconomic status among others.
- The Danish Civil Registration System⁹⁷ contains information on date of birth, sex, kinship (CPR number of parents and siblings), civil status and address.

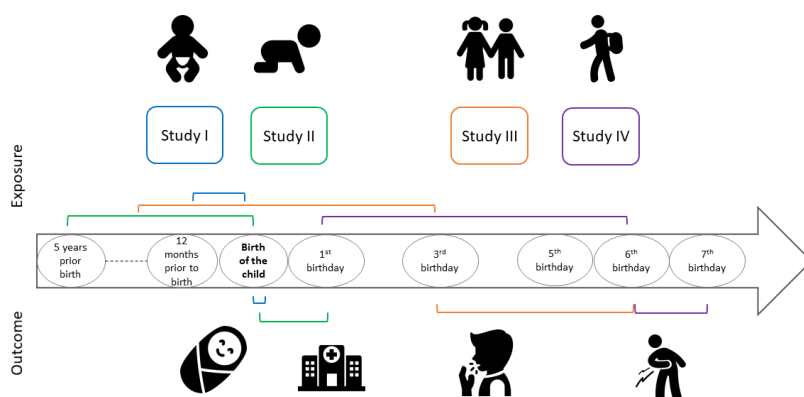
3.3. STUDY POPULATIONS AND DESIGN

Overall, the study population of this thesis was based on the CoVer-P (Children of Vulnerable Parents) cohort consisting of all children in Denmark born alive from 2000 to 2016. The cohort is based on information from the Danish nationwide registers with the aim of describing the health in children of vulnerable parents.

All children born in Denmark from 2000 to 2011, 2014 or 2016 were included in the studies. Figure 3 gives an overview of the exposure and outcome periods of each study.

In all four studies, the children were excluded if their parents did not live in Denmark at several time points during the exposure period, if the child or parents did not live in Denmark at baseline or if the parental personal identity number was missing, however for study I, these restrictions were imposed only for the mother's information and not both parents. Further study specific exclusion criteria are presented underneath.

Figure 3 Exposure and outcome periods of the four studies



3.3.1. STUDY I

Study I⁹⁸ included all live-born infants in Denmark born between January 1st, 2000 and December 31st, 2016. Infants were excluded if their mother was registered with a mental disorder due to psychoactive substance used (ICD-10 F1 diagnoses) during the exposure period.

3.3.2. STUDY II

In study II⁹⁹, all children born from January 1st, 2000 to December 31st, 2016 were included. The children were excluded if they died or emigrated during the first year of life or if they did not live with either parent after birth. The children were followed from birth and until their first birthday.

3.3.3. STUDY III

All children born from January 1st, 2000 to December 31st, 2014 were included in study III. Baseline was defined at date of the child's third birthday, and the child was followed until their sixth birthday, death, emigration from Denmark or March 15th, 2018, whichever came first.

3.3.4. STUDY IV

Study IV included all children born from January 1st, 2000 to December 31st, 2011. The children were followed from their sixth birthday and until their seventh birthday, death or emigration from Denmark, whichever came first.

3.4. MAIN EXPOSURE

The exposure in all four studies was parental mental health condition, except for study I where only maternal exposure was reported in the related article.

3.4.1. MENTAL HEALTHCARE IN DENMARK

There is no gold standard for categorising mental health conditions. Roughly, the level of mental healthcare in Denmark is based on the severity and complexity of the mental health condition (Figure 4). Therefore, the level of mental health care was chosen as the basis of categories used in this thesis.

According to the specialty guidance for psychiatry in Denmark¹⁰⁰, GPs take care of a broad spectrum of mental health conditions such as mild to moderate depression and anxiety, crises, dementia and alcohol abuse. Moreover, GPs take care of follow-up and control of certain psychiatric patients after assessment and treatment at psychiatric hospital¹⁰⁰. Patients with need of interdisciplinary effort and maybe a prolonged process are taken care of in the outpatient psychiatry¹⁰⁰.

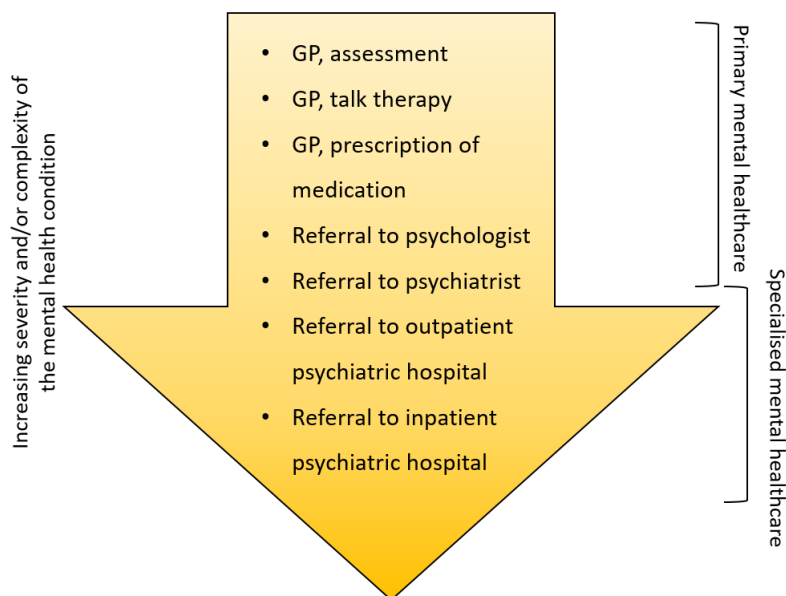
Practising psychologists primarily take care of patients exposed to a range of specific events and patients with mild to moderate depression or anxiety¹⁰⁰.

Practicing psychiatrists outside psychiatric hospital primarily take care of patients with mental health conditions of moderate severity with no need of interdisciplinary effort¹⁰⁰. The conditions are especially anxiety, depression, stress-related conditions, personality disorders and adults with ADHD (attention deficit hyperactivity disorder)¹⁰⁰.

Other mental health conditions such as schizophrenia, bipolar disorder, PTSD and moderate to severe cases of the above-mentioned conditions are taken care of at psychiatric hospital¹⁰⁰.

Arguments of the choice of the mental health condition severity groups are further described below. The criteria of the consensus definition of mental health conditions were carefully selected with contributions of specialists in psychiatry, general medicine and public health medicine and has also been used in other studies¹⁰¹.

Figure 4 Levels of mental healthcare^{102,103}



3.4.2. CLASSIFICATION OF MENTAL HEALTH CONDITIONS

Severe mental health condition

Some consistency across studies exists regarding a classification of severe mental illness. It is generally recognised that severe mental illness includes schizophrenia, bipolar disorder and depression^{8,104,105}. Bipolar disorder¹⁰⁵ and schizophrenia are less common and generally classified as severe. Contrarily, depression is common¹⁰⁶ and varies in severity¹⁰⁵. Admission to psychiatric hospital is recommended for the most severe cases of depression¹⁰³.

Borderline personality disorder is associated with maladaptive parenting¹⁰⁷ and impaired psychosocial function¹⁰⁸. Patients with severe borderline personality disorder are often admitted to psychiatric hospital¹⁰⁹, and this criterion was therefore added to capture these cases.

Moderate mental health condition

To differentiate less severe disorders treated by specialists from the disorders solely treated by GP and/or psychologist, a moderate group of mental health conditions was generated. In 2010, 184 specialists in psychiatry were working in private practice, mostly treating anxiety, affective and personality disorders and possibly treating up to 20% of the cases referred to psychiatric treatment⁹⁰. These patients are not registered in the Danish National Patient Register. However, any contact to practising specialist in psychiatry are registered in the Danish National Health Service Register for Primary Healthcare and was included. Further, all diagnoses of mental and behavioural disorders (ICD-10 F00-99) registered from psychiatric in- or outpatient contacts were included in this category, except the diagnoses described above in the severe category.

Minor mental health condition

The majority of all patients with depression are diagnosed and treated at GP¹¹⁰, and information hereof are not included in the Danish National Patient Register. The need of including other registers to identify depression is also described by Hvidberg et al¹¹¹ and Lyngsøe et al⁷⁶ among others.

Treatment with selective serotonin reuptake inhibitor (SSRI such as citalopram and fluoxetine) is the first-choice recommendation of medication for depression, and these cases are identified by including reimbursed prescriptions of SSRI from the National Prescription Register. The Danish National Prescription Register contains information on reimbursed prescriptions but not whether the medication was used. To capture parents who used the medication, a criterion of at least two prescriptions was added.

However, talk therapy solely and not medication is the recommendation for mild depression¹⁰³. Thus, mild depression will not be identified using the National Prescription Register and the Danish National Patient Register solely. Therefore, the services of talk therapy and psychometric tests at GP and contacts to psychologist were identified from the Danish National Health Service Register for Primary Healthcare. Therapy talk is a specific service with a specific service code for the GP. The service presupposes in advance agreed consultation and contains talk therapy with the use of relevant interview techniques and used for conditions such as depression and anxiety^{103,112}. Psychometric tests are also a specific service, an additional service in addition to a consultation, with a specific service code. The tests are used for diagnosing and monitoring of depression and anxiety among others^{103,112}.

Anxiety is another common condition mainly treated at GP¹¹². The first choice of treatment is cognitive behavioural therapy, either by GP (talk therapy) or psychologist after referral from the GP^{112,113}. SSRI and serotonin and norepinephrine reuptake inhibitor (SNRI such as venlafaxine and duloxetine) are first choice of pharmacotherapy¹¹². Benzodiazepines such as diazepam can be used preferably in a short period of time^{112,113}.

The criteria of exposure definition are summarised in Table 2.

Exposure period

Mental health conditions tend to be chronic or recur¹¹⁴, and a study examining chronic diseases classified all mental conditions as chronic conditions expected to be present for at least five years from the first identification in the register¹¹¹. Further, a Danish survey found that 75% of mental illness was still present after five years¹¹⁵. Moreover, Danish studies reported an increased risk of adverse health outcomes in children of mothers with not only recent and previous depression, but also past/post-depression^{56,73,116}. Therefore, a five-year exposure period was chosen. However, in study I an exposure period of 12 months prior to birth was chosen for the main analysis to capture the period close to prenatal period and a previous exposure period of 12-24 months prior to birth was supplementary examined.

Table 2 Exposure definition
Consensus definition of groups of mental health conditions

Exposure	Specification <i>At least one criterion fulfilled</i>	Further criteria <i>All criteria fulfilled</i>	Registry
Minor mental health conditions	Medication - At least 2 prescriptions of: <ul style="list-style-type: none"> antidepressant medicine (selective serotonin reuptake inhibitor (SSRI) ATC N06AB; serotonin- and norepinephrine reuptake inhibitor (SNRI) ATC N06AX) anxiolytic (benzodiazepines, ATC N03AE, N05BA, N05CD, N05CF) Services at general practice <ul style="list-style-type: none"> - At least two talk therapy - At least two psychometric tests 	No contacts to psychiatric hospital and no psychiatric hospital diagnoses No records of contact to private psychiatrist	Danish National Prescription Registry The Danish Health Service Register

	Other services - At least one contact to private psychologist	for Primary Care
<i>Moderate mental health conditions</i>	Any registered psychiatric diagnosis (ICD-10 F00-99) at psychiatric hospital, except the diagnoses included in the severe group (see below)	The National Patient Register
	Mental health conditions treated at psychiatrists outside psychiatric hospital (including child and adolescent psychiatrists)	The Danish Health Service Register for Primary Care
<i>Severe mental health condition</i>	Following ICD-10 diagnoses registered at psychiatric hospital: F20-22: Schizophrenia F30-31: Bipolar disease F32-34: Unipolar depression if also having a registered psychiatric inpatient admission F60.3: Emotionally unstable personality disorder if also having a registered psychiatric inpatient admission	The National Patient Register
Reference group	None of above - No registrations of psychiatric diagnoses and no mental health condition-related contacts to GP, psychologist or private psychiatrist and	
<i>No mental health condition</i>	- No prescriptions of antidepressants or anxiolytic drugs	

3.4.3. ADDITIONAL EXPOSURE

Socioeconomic position

In study III, socioeconomic position (SEP) was based on a variable from the Income Statistics Register⁹⁶ describing the main source of income or employment. The variable was dichotomised in disadvantaged socioeconomic position, having no

affiliation to the labour market or education (such as receiving disability pension, cash benefits or similar), or not (such as being self-employed or employee).

Preventive child health examination

Preventive child health examination (PCHE) attendance was used in study IV. In Denmark, all children are offered seven PCHEs the first five years of life. The first three examinations are during the first year followed by one examination a year at the age of two, three, four and five. In study IV, the last four examinations were included. The PCHEs were categorised in three: Attending all or missing one, missing two or three and missing all four examinations.

3.5. OUTCOMES

Study I

The primary outcomes of study I⁹⁸ were neonatal mortality (the first 28 days of life), five-minute Apgar score below seven, five-minute Apgar score below four and hospital admission during the neonatal period for at least one night.

The secondary outcomes were defined as an ICD-10 diagnosis of respiratory distress syndrome (P22), abstinence syndrome (P961-62), hypoglycaemia (P703-04), neonatal seizures (P90), neonatal bacterial sepsis (P36), jaundice (P590, P598-99) and feeding problems, dehydration and/or failure to thrive (P920-23, P925-29, P741, P742A, P818A, R628A).

Study II

The outcomes of study II⁹⁹ were defined as healthcare service contacts during the first year of the life. GP daytime and out-of-hour contacts were defined as either consultation, telephone contact or physical visit. Vaccinations and PCHEs were not included. As mentioned in the section 3.1., the Capital Region has had its own coverage system of out-of-hour medical service since 2014⁸⁷. These data were not available and therefore children from this region were excluded from the out-of-hour analysis from 2014-2016.

Any registered admission to hospital and contact to outpatient unit was defined as an inpatient respectively outpatient contact. Only outpatient contacts after the neonatal period were included due to changes in registration of neonatal outpatient contacts during the study period. An emergency department (ED) contact was defined as any registered contact to the emergency department.

Study III

Child asthma was the outcome of study III and was based on asthma medication from the Danish National Prescription Register and diagnosis from the Danish National Patient Register and defined as at least two redeemed prescriptions of either inhaled long-acting β 2-agonist (ATC R03AC), fixed-dose combinations of inhaled β 2-agonists and corticosteroids (ATC R03AK), inhaled corticosteroids (ATC R03BA) or leukotriene-receptor antagonist (ATC R03DC) and/or a primary or secondary hospital diagnosis of asthma (ICD-10 J45) or status asthmaticus (ICD-10 J46).

Study IV

In study IV, the outcome of functional gastrointestinal disorder (FGID) in children was defined using paediatric, clinical guidelines¹¹⁷ and the Rome IV-criteria⁷⁰. The ICD-10 diagnoses used were: nausea and vomiting (DR11); functional dyspepsia (DK30); irritable bowel syndrome (DK58); abdominal pain (DR100-108); other specified general symptoms and signs, gastrointestinal (R688A9B2); constipation (DK590); faecal incontinence (DR15) and gastro-oesophageal reflux disease without oesophagitis (DK219).

3.6. COVARIATES

All covariates were extracted at baseline except for family income, which was extracted the calendar year before baseline (study II⁹⁹).

Table 3 Covariates included in the four studies

Covariate	Details	Register	Used in studies:
Parental covariates			
Education	Using the International Standard Classification of Education (ISCED 2011), grouped in three according to highest completed education: 1) Early childhood education (ISCED levels 0–2) 2) General upper secondary education, e.g. high school programs (ISCED 3–4) 3) Short-, medium-length or long-length higher education, e.g. tertiary	The Population Education Register ⁹⁴	I, II, III, IV

	education, bachelor, Master's, PhD (ISCED 5–8)		
Age	Continuous	Danish Civil Registration System ⁹⁷	I, II, III, IV
Asthma	Dichotomous: Yes or no ICD-10: DJ45-46	Danish National Patient Register ⁸⁹	III
Cohabitation	Dichotomous: Cohabiting or not	Danish Civil Registration System ⁹⁷	I, II, III, IV
Mental health of the other parent	Mental health condition defined in the 'Exposure' section		III, IV
Maternal smoking during pregnancy	Dichotomous: Smokers and non-smokers. Mothers were considered non-smokers if they did not smoke during pregnancy or stopped smoking during the first trimester ¹¹⁸	The Danish Medical Birth Register ⁹³	I
Gestational diabetes	Yes/no ICD-10 DO244	Danish National Patient Register ⁸⁹	I
Household income	Continuous Equivalated disposable income for the family, which took into account the number of children and adults in the household	The Income Statistics Register ⁹⁶	II
Parity	Dichotomous: First child of the mother or not	The Danish Medical Birth Register ⁹³	II
Child-related covariates			
Sex	Dichotomous: Male or female	Danish Civil	IV

		Registration System ⁹⁷	
Gestational age	Continuous	Danish National Patient Register ⁸⁹	I
Country of origin	Grouped in three: Nordic, other Western Europe and non-Western countries	Danish Civil Registration System ⁹⁷	I, IV
Municipality	Grouped in four: outer, rural, intermediate and city	Danish Civil Registration System ⁹⁷	IV
Other			
Calendar year	Continuous	Danish Civil Registration System ⁹⁷	I, II, III, IV

To minimize residual confounding when adjusting for a continuous variable¹¹⁹, restricted cubic splines with three knots were chosen when adjusting for parental age, family income, calendar year and gestational age.

3.7. METHODS OF ANALYSIS

In all four studies, baseline characteristics were presented as numbers and percentages of the covariates by parental mental health condition.

All studies compared outcomes for the children of parents with mental health conditions to children of parents without mental health conditions.

The adjusted regression analyses in all four studies was complete case analyses.

Siblings appeared in all four cohorts and should preferably be treated as dependent. In study I, III and IV, the estimates were fitted using generalized estimating equations with an exchangeable correlation structure in which the correlation between a pair of observations in the same cluster (such as full siblings) is assumed to be the same for all pairs in each cluster¹²⁰. In study I, siblings were defined as half-siblings by the mother only. In study III and IV, siblings were defined as full siblings by the mother

and the father. The issue of siblings in study II was handled by controlling for parity and performing a sensitivity analysis only including first-born children.

3.7.1. STUDY I

Due to the rarity for some of the primary outcomes (neonatal mortality and Apgar score <4), moderate and severe mental health conditions were combined in one category.

In study I, a generalised linear model based on a Poisson distribution with robust estimation of standard errors was chosen, and results were presented as adjusted risk ratios (RR) for each perinatal outcome with 95% confidence intervals (CI). Further, a subgroup analysis was performed to estimate the risks of maternal mental health conditions across subtypes.

Two sensitivity analyses were performed. First, an analysis with two mutually exclusive exposure periods was made, one period of active mental health condition measured 0-12 months prior to birth and another of previous mental health condition measured 12 to 24 months prior to birth. To further examine whether the presence of siblings affected the results, a sensitivity analysis including only first-born infants was made⁹⁸.

3.7.2. STUDY II

Due to too few observations when combining maternal and paternal mental health into one categorical variable, moderate and severe mental health conditions were combined in one category. In study II, the exposure was the eight different combinations of parental mental health condition (e.g. maternal none and paternal minor mental health condition; both parents with minor mental health conditions and so forth) compared to the reference of both parents without mental health conditions.

Due to overdispersion in the data, negative binomial regression was chosen and applied to the number of outcome events. Results were presented as number of each outcome of interest, incidence rates and adjusted incidence rate ratios (IRR).

Three sensitivity analyses were performed. First, as siblings appeared in the cohort, a sensitivity analysis examined whether they affected the results including only first-born children of the mothers in the analysis. Second, non-fatal birth defects, prematurity and other significant conditions in early life might necessitate a higher number of healthcare contacts during the first year of life. To examine whether such conditions affected the estimates, a sensitivity analysis was performed excluding children admitted for at least 1 week during first month of life. Finally, a sensitivity analysis in different strata of calendar years was performed to examine whether the effects might differ over time⁹⁹.

3.7.3. STUDY III

Maternal and paternal mental health conditions were handled as separate exposures and adjusted for one another.

Due to overdispersion in the data, negative binomial regression was chosen and applied to the number of outcome events. Results were presented as number of each outcome of interest and adjusted incidence rate ratios (IRR).

An interaction analysis was performed to evaluate whether poor parental mental health (none, minor, moderate, severe) and disadvantaged socioeconomic position (SEP0, SEP1) interacted on the risk of asthma outcome. As the aim was to use a public health relevant measure, interaction on additive scale was examined using the relative excess risk of interaction, RERI¹²¹, such as:

$$RERI_{minor} = \frac{IRR_{minor,SEP1} - IRR_{minor,SEP0} - IRR_{none,SEP1} + IRR_{none,SEP0}}{IRR_{none,SEP0}}$$

Subgroup analyses within each level of mental health condition were performed; for minor mental health conditions based on mental health services and prescriptions of medication, for moderate and severe mental health conditions based on diagnoses.

To examine whether chronic conditions in early childhood, e.g. chromosome anomalies and birth defects had an impact on the association between child asthma and poor parental mental health, a sensitivity analysis was performed excluding children with a diagnosis prior to baseline. Further, an analysis with the outcome separate as either asthma medication or asthma diagnosis was performed.

3.7.4. STUDY IV

Maternal and paternal mental health conditions were handled as separate exposures and adjusted for one another.

Due to overdispersion in the data, negative binomial regression was chosen and applied to the number of outcome events. Results were presented as number of each outcome of interest and adjusted IRRs.

To examine whether PCHE participation was associated with a subsequent risk of a hospital diagnosis of FGID, the IRRs were calculated in the strata of parental mental health condition with PCHE participation as independent variable. Due to low observation counts in these strata, moderate and severe mental health conditions were combined into one category for these analyses.

As the risk of FGID diagnosis might differ between acute and planned hospital contacts, a sensitivity analysis was made for FGID diagnosis from hospital admissions

and outpatient contacts separately. To examine whether a FGID diagnosis before baseline affected the results, a sensitivity analysis was made excluding these children. Further, an analysis in different strata of calendar years was performed.

3.7.5. ADDITIONAL ANALYSES FOR THE THESIS

Two additional analyses were made. First, to examine whether the same parents appeared in the exposure groups of the different studies, children included in all four studies were identified. From this population, the overlap of the different exposure groups through the four studies was calculated dichotomising the exposure into exposed to maternal respectively paternal mental health condition (yes/no). The overlap of exposure groups in the four studies was presented as a proportional Venn diagram.

In the second analysis, the study populations from the specific studies were used. The risks for maternal and paternal, respectively, minor, moderate and severe mental health conditions of the primary outcomes of study I and II were calculated. The results were presented as IRRs adjusted for the covariates used in the specific study and the mental health of the other parent. The estimates were presented in one, collecting figure (Figure 7) also illustrating the already calculated results from study III and IV.

Software

Data was analysed using STATA SE version 15.1 and 16.1 at Statistics Denmark remote server.

3.8. ETHICS AND REGULATIONS

The Danish Act on Processing of Personal Data provides the legal basis to retain individually identifiable health data for research purposes¹²². For research purpose, informed consent from the study subjects are not required. Only researchers and analysts from research environments pre-approved by Statistics Denmark can be granted access to data¹²³. Further, the project requires approval from Statistics Denmark, and data is deidentified before the researcher can get access to the data via a secure remote access to servers at Statistics Denmark¹²³. Moreover, when using medication data, approval from the Danish Health Data Authority is required.

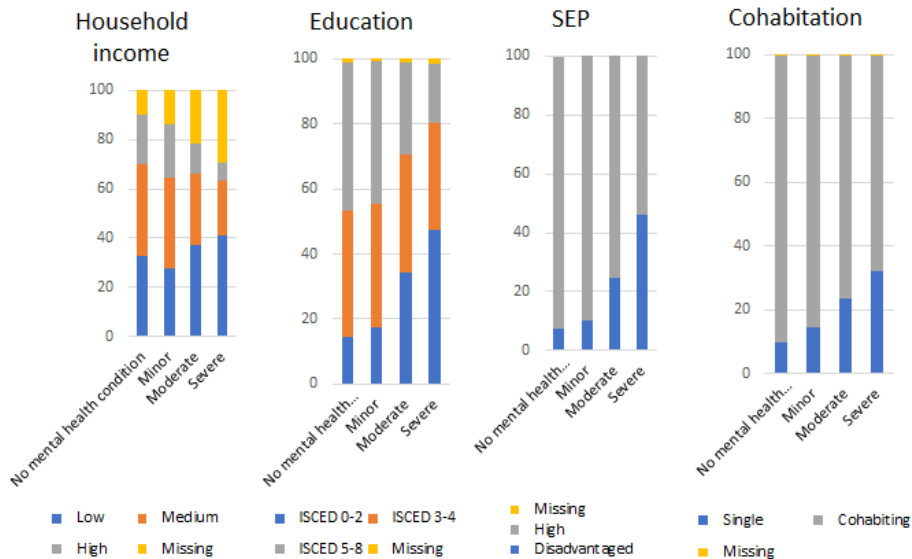
This thesis is based on a project approved by Statistics Denmark (project 707196). Ethical approval is not needed for register research studies in Denmark¹²². The project is registered by the North Denmark Region (project ID number 2019-78).

CHAPTER 4. RESULTS

This chapter summarises results from the four studies. Further details, such as flow charts of the study populations and more details on baseline characteristics, might be found in the individual article (appendices A-D).

For all four studies, children of parents with mental health conditions more often also had parents with educations of shorter lengths, not cohabiting, with no affiliation to the labour market and/or education and with lower household income than children of parents without mental health conditions. Figure 5 illustrates the socioeconomic characteristics of study II. The characteristics were similar in the four studies, though the share of parents with low income and shortest education (ISCED 0-2) were smaller in study III and IV.

Figure 5 Socioeconomic characteristics by exposure status in study II



SEP: Socioeconomic position. Disadvantaged: No affiliation to the labour market or education (such as receiving disability pension, cash benefits or similar)

4.1. STUDY I

In study I, using a 12 months period of mental health condition, 4.0% of the infants in the study population had a mother with minor and 2.9% had a mother with moderate-

severe mental health condition (Table 2 in Appendix A). The prevalence of smoking during pregnancy was 12%, 17% and 22% in mothers with no, minor and moderate-severe mental health conditions, respectively⁹⁸.

Figure 2 and 3 in Appendix A presents unadjusted and adjusted RRs of the association between minor and moderate-severe mental health condition by the mother and the primary and secondary perinatal outcomes of the infants⁹⁸.

Further, the results of the supplementary analysis of the association between the primary outcomes and minor, moderate and severe mental health condition separately of both the mother and the father is presented in Figure 7.

Minor and moderate-severe mental health conditions in the mother were associated with increased risk of the all outcomes; however, the rare outcomes of neonatal mortality and Apgar score <4, and further jaundice were without statistically significance (Figure 7 and Appendix A: Figure 2 and Figure 3)⁹⁸.

For most outcomes, a stronger association was seen for moderate-severe than for minor mental health conditions. For neonatal seizures, the association with minor mental health condition (RR 1.53 (95% CI 1.23-1.90)) was stronger than for moderate-severe mental health condition (RR 1.34 (95% CI 1.02-1.75)). For more outcomes, such as hospital admission, hypoglycaemia and sepsis, the associations were similar for minor and moderate-severe mental health condition (hospital admission minor RR 1.20 (95% CI 1.17-1.23), moderate-severe RR 1.22 (95% CI 1.19-1.26)). However, when examining moderate and severe mental health conditions separately, an even stronger association was seen for severe mental health condition (RR 1.32 (95% CI 1.19-1.46))⁹⁸.

An extra-strong association was seen for neonatal abstinence syndrome (minor: RR 10.30 (95% CI 8.40-12.63) and moderate-severe: RR 12.63 (95% CI 10.17-15.67))⁹⁸.

An analysis of subgroups within the minor and moderate-severe groups found risk estimates similar to those of the main analyses (Table 3 in Appendix A). However, stronger associations were seen in infants of mothers with at least two redeemed prescription antidepressants and/or benzodiazepines⁹⁸.

Two sensitivity analyses were performed. The first examined previous maternal mental health condition using an exposure period 24-12 months prior to birth and found weakened association only statistically significant for hospital admission, minor: adjusted RR 1.13 (95% CI 1.10-1.17); moderate-severe: adjusted RR 1.13 (95% CI 1.07-1.20) (Supporting Information Table S1 in Appendix A). The second included only first-born infants and found results corresponding the results of the main analysis. However, some estimates were a bit higher than those of the main analysis (Supporting Information Table S2 in Appendix A)⁹⁸.

4.2. STUDY II

Using a five-year exposure period in study II, 11% and 8% of the mothers were classified with minor and moderate-severe mental health conditions, respectively. For the fathers, the percentages were eight and five percent, respectively (Table 2 in Appendix B)⁹⁹.

Both maternal and paternal mental health conditions were associated with increased risk of all five outcomes of healthcare utilisation during the child's first year of life (Table 4 and Table 7)⁹⁹. For all outcomes, the associations were stronger for maternal moderate-severe mental health conditions than minor; for example, the risk of inpatient contacts was increased by 25% for maternal minor and father no mental health condition (IRR 1.25 (95% CI 1.24-1.27)) and by 39% for maternal moderate-severe and father with no mental health condition (IRR 1.39 (95% CI 1.36-1.41)) compared the reference group (Table 4)⁹⁹.

Overall, the associations were stronger if both parents were classified with a mental health condition than if one parent was classified with no mental health condition. For example, the risk of inpatient contacts was increased by 25% if the mother was classified with minor and the father with no mental health condition (IRR 1.25 (95% CI 1.24-1.27)). If both parents were classified with minor mental health condition, the risk of inpatient contacts was increased by 33% (IRR 1.33 (95% CI 1.29-1.37)). If only the father was classified with minor and the mother with no mental health condition, the risk was increased by 11% (IRR 1.11 (95% CI 1.08-1.13))⁹⁹.

The associations of maternal mental health was overall stronger than for paternal mental health except for emergency department contacts, where both maternal and paternal minor mental health condition, respectively, and the other parent without mental health condition was associated with an increased risk of 14% (mother IRR 1.14 (95% CI 1.11-1.18); father IRR 1.14 (95% CI 1.10-1.19))⁹⁹.

Three sensitivity analyses were performed, the first including only first-born, the second excluding children with at least one week of admission during the first month of life and the third stratified in four different time periods (Supplementary table 4-6 in Appendix B). Neither of analyses yielded results markedly different the those of the main analyses⁹⁹.

Table 4 Adjusted IRRs (95% CI) of each outcome of use of healthcare service for each group of mental health condition during the child's first year of life**Adjusted IRRs (95% CI) of GP contacts daytime** for each combination of maternal and paternal mental health condition

		Mother		
	Mental health condition	None	Minor	Moderate-severe
	None	Reference	1.17 (1.17 - 1.18)	1.18 (1.17 - 1.19)
Father	Minor	1.06 (1.05 - 1.07)	1.22 (1.21 - 1.24)	1.25 (1.23 - 1.27)
	Moderate-severe	1.05 (1.04 - 1.06)	1.17 (1.15 - 1.19)	1.18 (1.16 - 1.20)

Adjusted IRRs (95% CI) of out-of-hour contacts for each combination of maternal and paternal mental health condition N = 764012 (84%)

		Mother		
	Mental health condition	None	Minor	Moderate-severe
	None	Reference	1.26 (1.25 - 1.28)	1.39 (1.37 - 1.41)
Father	Minor	1.15 (1.14 - 1.17)	1.37 (1.34 - 1.41)	1.49 (1.45 - 1.54)
	Moderate-severe	1.20 (1.18 - 1.22)	1.36 (1.31 - 1.41)	1.44 (1.40 - 1.49)

Adjusted IRRs (95% CI) of emergency department contacts for each combination of maternal and paternal mental health condition N = 810478 (84%)

		Mother		
	Mental health condition	None	Minor	Moderate-severe
	None	Reference	1.14 (1.11 - 1.18)	1.36 (1.31 - 1.41)
Father	Minor	1.14 (1.10 - 1.19)	1.25 (1.17 - 1.34)	1.39 (1.27 - 1.52)
	Moderate-severe	1.31 (1.25 - 1.38)	1.27 (1.15 - 1.41)	1.35 (1.24 - 1.47)

Adjusted IRRs (95% CI) of inpatient contacts for each combination of maternal and paternal mental health condition N = 810478 (84%)

		Mother		
Mental health condition		None	Minor	Moderate-severe
Father	None	Reference	1.25 (1.24 - 1.27)	1.39 (1.36 - 1.41)
	Minor	1.11 (1.08 - 1.13)	1.33 (1.29 - 1.37)	1.48 (1.43 - 1.54)
	Moderate-severe	1.12 (1.10 - 1.15)	1.26 (1.21 - 1.32)	1.41 (1.36 - 1.47)

Adjusted IRRs (95% CI) of outpatient contacts for each combination of maternal and paternal mental health condition N = 810478 (84%)

		Mother		
Mental health condition		None	Minor	Moderate-severe
Father	None	Reference	1.22 (1.19 - 1.25)	1.29 (1.25 - 1.33)
	Minor	1.07 (1.04 - 1.11)	1.27 (1.20 - 1.35)	1.59 (1.47 - 1.72)
	Moderate-severe	1.12 (1.07 - 1.17)	1.21 (1.10 - 1.32)	1.47 (1.36 - 1.59)

Adjusted for calendar year, sex, parental age, parental education, family income, family type and parity

Complete case analysis based on 84 % of the study population

Table adapted from Heuckendorff et al 2021⁹⁹

4.3. STUDY III

In study III, 17%, eight percent and one percent of the mothers were classified with minor, moderate and severe mental health conditions, respectively. For the fathers, the percentages were 11, five and one percent, respective (Table 1 in Appendix C).

Both maternal and paternal mental health conditions were associated with an increased risk of asthma in children aged three to five (Figure 7 and Appendix C, Figure 2).

The strongest association was seen for maternal exposure, whereas for the father the associations were only small (minor: IRR 1.15 (95% CI 1.14-1.16) and moderate: IRR 1.05 (95% CI 1.03-1.07)) or without statistical significance (severe mental health condition: IRR 1.03 (95% CI 0.99-1.07)) (Figure 7).

For maternal exposure, the risk of asthma increased slightly with the severity of mental health condition. For minor mental health condition, the risk was increased by 35% (IRR 1.17 (95% CI 1.34-1.36)), for moderate by 34% (IRR 1.34 (95% CI 1.33-1.36)) and severe by 38% (IRR 1.38 (95% CI 1.34-1.43)).

The analysis of interaction showed additive interaction with an excess risk of asthma for the combination of poor mental health of the mother and disadvantaged socioeconomic position, RERI 0.07 for minor (95% CI 0.04-0.11), RERI 0.08 for moderate (95% CI 0.05-0.12) and RERI 0.21 for severe mental health condition (95% CI 0.12-0.30) (Appendix C: Table 2).

Two sensitivity analyses were performed, one excluding children with chronic conditions in early childhood and one analysing the outcome separate as either asthma medication or asthma diagnosis (eTable 1 and 2 in Appendix C). Overall, the estimates of both analyses were similar to those of the main analysis.

4.4. STUDY IV

In study IV, 24%, 12% and two percent of the children had at least one parent with minor, moderate and severe mental health condition, respectively (Appendix D: Table 1). For children of parents with minor, moderate and severe mental health conditions, 1.4%, 1.6% and 1.7% had a hospital FGID diagnosis during the follow-up period. Among children of parents without a mental health condition, 1.0% a diagnosis of FGID.

Parental mental health condition was associated with an increased risk of FGID in the children (Figure 7, Appendix D: Figure 2). The strongest association was seen for maternal exposure with an increase of 36% (IRR 1.36 (95% CI 1.30-1.42)) for minor mental health condition, 57% (IRR 1.57 (95% CI 1.49-1.66)) for moderate and 58% (IRR 1.58 (95% CI 1.38-1.81)) for severe mental health condition compared to no mental health condition. The magnitude of association was less for children exposed to poor mental health of the father (minor: IRR 1.10 (95% CI 1.04-1.16), moderate: IRR 1.14 (95% CI 1.06-1.22) and severe: IRR 1.13 (95% CI 0.96-1.32)).

PCHE participation was associated with an increased risk of FGID, compared to not participating, both in the overall population and in all strata of mental health conditions (Appendix D, Figure 3). Using ‘missing all PCHE’ as reference, the risk of FGID was increased by 15% (IRR 1.15 (95% CI 1.02-1.30)) in children who attended all/missed one PCHE and had mothers with no mental health condition. For children of mothers with minor mental health conditions, the risk of FGID was increased by 24% (IRR 1.24 (95% CI 1.02-1.49)) and by 30% (IRR 1.30 (95% CI 1.06-1.60)) in children of mothers with moderate-severe mental health conditions. The same trends were seen for paternal exposure; however, the estimates did not reach statistical significance.

Three sensitivity analyses were made; the first examining FGID diagnoses from outpatient and inpatient hospital contacts separately (Supplementary table 1 in Appendix D), the second excluding children with a hospital diagnosis of FGID prior to baseline (Supplementary table 2 in Appendix D), and the third analysis stratified in three time periods (Supplementary table 3 in Appendix D). The two first analyses yielded estimates similar to those of the main analysis. The third showed an increase of the number of children with a FGID diagnosis through the three time periods, and the association between parental mental health conditions and child FGID was stronger in the last period.

4.5. ADDITIONAL ANALYSES

The overlap between the exposure groups across the four studies were examined and illustrated in Figure 6 (details presented in Supplementary table 1). The exposure groups of study I were 100% included in the exposure groups of study II and III as the period of exposure in study I was only 12 months. For the other three studies, the exposure periods were five years. Almost three quarters of the study I exposure group was included in the study IV exposure group. In study II, 80% of the exposure group was also a part of the exposure group in study III and almost two thirds in study IV for the mothers and more than half of the fathers.

Figure 6 Proportional Venn diagram illustrating the overlap between the exposure groups in the four studies

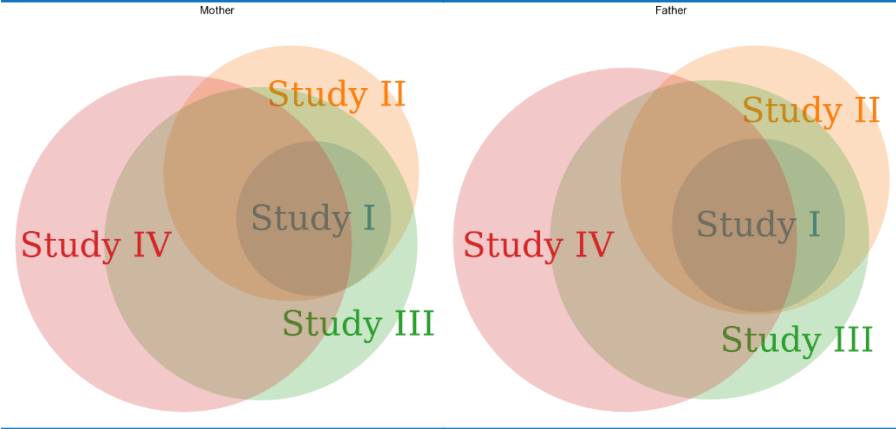
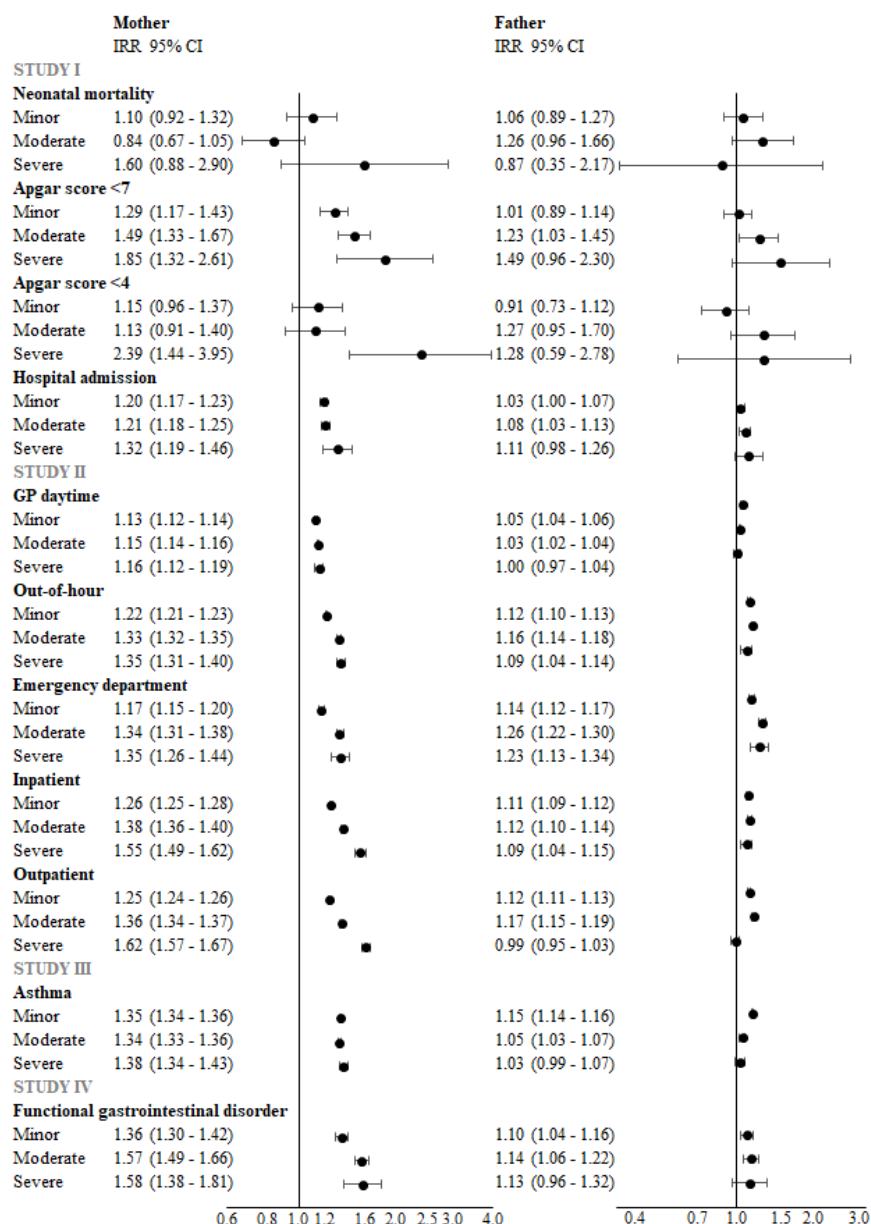


Figure 7 Results of the association between maternal and paternal exposure (minor, moderate, severe mental health condition) and the main outcomes of all four studies.

Children of parents with mental health conditions were compared to children of parents without (reference).



In study I the RRs were adjusted for calendar year, parental age, education, cohabitation, country of origin, maternal smoking during pregnancy, gestational age, gestational diabetes and mental health of the other parent

In study II the IRRs were adjusted for calendar year, sex, parental age, parental education, family income, cohabitation and mental health of the other parent

In study III the IRRs were adjusted for calendar year, parental age, education, cohabitation status, mental health of the other parent and mother and father asthma

In study IV the IRRs were adjusted for child sex, calendar year, parental age, education, cohabitation, country of origin, municipality and mental health of the other parent

A trend toward an association between mental health of the father and adverse perinatal outcomes was seen with stronger associations with increasing severity of the mental health condition; however, the estimates did not reach statistical significance (Figure 7).

CHAPTER 5. DISCUSSION

5.1. DISCUSSION OF RESULTS

5.1.1. KEY RESULTS

The share of exposed children ranged from 6.9% of the children in study I with a mother with mental health condition 0-12 months prior to birth to 38% of the children in study IV with at least one parent with mental health condition in study IV.

Minor, moderate and severe mental health conditions of the parents were associated with an increased risk of morbidities from birth and throughout early childhood.

Minor and moderate-severe maternal mental health conditions were associated with increased risk of several perinatal outcomes. A trend toward an association; however, not statistically significant, was found between mental health of the father and adverse perinatal outcomes. The first year of the child's life minor and moderate-severe mental health conditions of both mother and father were associated with increased healthcare utilisation for all the five types of healthcare services. From the age of three up to and including five years, increased risk of asthma was reported in children of mothers with minor, moderate and severe mental health conditions along with an excess risk in children of mothers with both mental health conditions and socioeconomic disadvantage. At the age of six increased risk of functional gastrointestinal disorder was found in children of parents with minor, moderate and severe mental health conditions. Attendance at preventive child health examinations was associated with an increased risk of functional gastrointestinal disorder both in the overall population and within strata of parental mental health conditions.

This chapter will discuss the findings of the four studies of this thesis. The findings will be interpreted and results from similar studies will be discussed. This will be followed by a discussion of the methodological strengths and limitations of the thesis.

5.1.2. STUDY I

The aim of study I was to investigate neonatal outcomes in infants of mothers with mental health conditions⁹⁸. The most severe of the primary outcomes was neonatal mortality, a rare outcome of which the existing evidence is conflicting⁹⁸. As for other studies^{46,124}, the results of study I was without statistical significance. A trend towards an increased risk was seen for minor and severe mental health conditions, and a decreased risk for moderate mental health conditions (Figure 7). Nevertheless, a systematic review and meta-analysis found a pooled OR 1.67 (95% CI 1.26-2.22) in

infants of mothers with mental health conditions including bipolar disorder, major depressive disorder, depression, depressive symptoms, affective disorders, severe mental illness, schizophrenia and alcohol-related disorders⁵⁴ and might indicate that a cautious interpretation towards an association can be made.

The findings of this study extended on existing knowledge showing not only moderate to severe mental health conditions requiring specialised mental healthcare, but also minor mental health conditions treated solely at primary care settings were associated with an increased range of adverse perinatal outcomes.

The mechanisms underlying the association between maternal mental health conditions and neonatal outcomes are highly complex and likely including several pathways. Neuroendocrine factors, including elevated levels of cortisol corticotrophin releasing hormone and norepinephrine and low levels of serotonin and dopamine, has been described as potential mediators of the relationship between maternal depression and outcomes such as lower birthweight and shorter gestational age^{39,125}, which may further lead to adverse neonatal outcomes such as lower Apgar-scores and neonatal mortality.

Moreover, the psychosocial pathway, as described in section 1.3., may be important when unravelling the association between maternal mental health conditions and adverse neonatal outcomes. Fear of being judged, of having an impact on the baby, of deterioration of mental health and of being reported to social services are described in pregnant women and parents of infants³⁰. Stigmatisation and fear might act through neuroendocrine pathways of which some may be described above.

The evidence of the impact of exposure periods of maternal mental health condition on perinatal outcomes are diverse; One study indicated that chronic rather than acute depression affected infant health³⁹. New-borns of mothers with dysthymic versus major depression had a significantly shorter gestational age, lower birthweight, shorter birth length and more obstetric complications³⁹. Another study reported that only active (0-12 months prior to birth) and not previous (12-24 months prior to birth) PTSD increased the risk of preterm birth⁴⁸. The results of the sensitivity analysis of study I of active (0-12 months prior to birth) and previous (12-24 months prior to birth) mental health conditions indicated an effect not related to in utero exposure but also suggested an impact of general psychosocial vulnerability⁹⁸.

5.1.3. STUDY II

The aim of study II was to examine the use of healthcare service in children of parents, both mother and father, with mental health conditions⁹⁹. In line with several studies examining maternal depression^{56,58–60,62,126} including a Danish study⁵⁶ that to some

extend was based on the same population as this study, study II reported increased rates of healthcare use in the children.

This study extended existing knowledge with a design including data from primary and secondary healthcare settings examining the use of a broad range of healthcare service in a large population. The association persisted for all types of contacts and all combinations of minor and moderate-severe mental health conditions of the mother and father. Overall, existing studies only included the mental health of the father as a covariate for which adjustments were made^{56,60,127} or not at all^{57-59,61}. This study contributed in the knowledge gap by showing that paternal mental health conditions for most outcomes were associated with increased use of child healthcare utilization; however, less than for maternal exposure⁹⁹. For all outcomes, the risks were smaller if only one parent was classified with and the other parent without mental health conditions than if both parents were classified with a mental health condition. This finding can be interpreted as a potential protective effect of having a ‘mentally healthy’ parent⁹⁹.

The ‘appropriate’ amount of healthcare use is not addressed in the literature and cannot be examined via information from the registers. A higher rate of healthcare contacts may mirror a different pattern of healthcare utilisation in exposed children rather than poor health. Mental health conditions might be related to lower parenting self-efficacy¹²⁸ and a higher need of supervision from health professionals. Moreover, GPs might be more likely to schedule extra consultations for exposed children and refer to assessment at hospital¹²⁹. In these cases, increased healthcare use is not necessarily negative but might reflect appropriate handling by the GP.

However, the findings of this study could also reflect poorer health in exposed children. This is supported by several other studies. As mentioned in section 1.5.2., morbidity in children the first year of life is primarily characterised by infections and especially upper airway infections account for at large share the healthcare contacts to both GPs and hospitals⁵⁵. This is confirmed by Lyngsøe and colleagues that found more positive tests of C-reactive protein⁵⁶ and further corroborating with a UK study reported higher risk of gastrointestinal infections and lower respiratory tract infections in young children of mothers with perinatal depression¹³⁰. Thus, a higher rate of infections in children of parents with mental health conditions could explain some of the increased healthcare utilisation in study II.

Moreover, injuries are likely to contribute to the increased healthcare use the first year of life in children of parents with mental health conditions, as a study reported higher rates of injuries, also in the first year of life, in children of parents with mental illness¹³¹. The rate of any injury was increased by 27% for any mental illness of the father and by 31% for any mental illness of the mother¹³¹. Thus, higher rates of injuries in exposed children may explain some of the observed healthcare use in study II.

Therefore, it seems reasonable to hold on to the interpretation that the findings of this study are, at least partly, evidence of higher risk of morbidity, such as infections and injuries, in children of parents with mental health conditions.

5.1.4. STUDY III

The aim of study III was to investigate the associations between parental mental health conditions and child asthma and further, to explore whether parental mental health conditions interacted with disadvantaged socioeconomic position.

The findings of study III support the trend in the field of higher risks of asthma in children of mothers with depression/anxiety⁷, mothers with prenatal psychological stress¹³² and two other studies examining respiratory illness in children of parents with severe mental illness^{9,12}. This study's findings contribute with new knowledge regarding the influence of different severities of mental health conditions; minor, moderate and severe mental health conditions yielded similar effect on child asthma.

As mentioned in section 1.4., parental mental health conditions and disadvantaged socioeconomic conditions may have a negative impact on each other. Both factors are further described related to child health and may influence morbidity in early childhood via a psychosocial pathway. Parental mental health conditions and socioeconomic disadvantaged conditions may lead to immune dysregulation in the child¹³³. In utero as well as early childhood exposure seem to lead to disturbed regulation of stress systems, such as the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal-medullary system, which further modulate the immune function in the child^{39,134}. The rapid growth and the plasticity of the respiratory system may make the foetus and young children particularly vulnerable to the early exposures with transient as well as long-term effects¹³⁴.

The negative mutual impact that disadvantaged socioeconomic conditions and mental health conditions may have might explain the results of the interaction analysis with extra high risks in the children exposed to both. Moreover, this finding of additive interaction highlights a group of children (and parents) that might particularly benefit from preventive interventions.

Pregnant women with mental health conditions are more likely to smoke than pregnant women without as shown in study I (Appendix A, table 2), and people, in general, with poor mental health are more likely to smoke than people without¹⁸. Also socioeconomic disadvantage have been reported as a predictor of children's exposure to second-hand smoke at home¹³⁵, which is a risk factor of childhood asthma¹³⁶. Smoking may therefore mediate the association between mental health conditions and disadvantaged socioeconomic positions and child asthma.

Smoking might be a mediator between parental mental health conditions and child morbidity as well as disadvantaged socioeconomic conditions and child morbidity, and further, an identifiable and modifiable factor. The desire for smoking cessation is similar among people with and without mental disorder¹³⁷. A recent report from the Danish Health Authority highlights the importance of integrating smoking cessation with psychiatric treatment as smoking cessation and smoking cessation medication is not associated with worsening of symptoms, contrarily, several studies indicate an improvement of psychiatric symptoms with prolonged abstinence³⁴. Currently, pregnant women and parents who smokes are offered the same smoking cessation interventions as the general population regardless of concurrent issues. Therefore, tailored smoking cessation interventions for pregnant women, upcoming fathers and parents who smoke might be considered. The findings of this study further emphasise the importance of legislation regarding smoking to protect children from second-hand smoking¹⁵.

5.1.5. STUDY IV

The aim of study IV was to investigate the association between parental mental health conditions and functional gastrointestinal disorder (FGID) in the children and, further, to examine the association between preventive child health examination (PCHE) participation and FGID in the overall population and within strata of parental mental health conditions.

The prevalence of a hospital diagnosis of FGID in study IV was markedly lower than the overall prevalence reported by other studies^{69,70,138}. However, it should be noted that study IV not included cases of FGID solely treated in primary care, as this information is not available. Further, this study only followed the children for one year.

The results of associations between minor, moderate and severe mental health conditions and increased risk of hospital diagnoses of FGID in the children are supported by earlier findings; Ramchandani and colleagues reported association between anxiety of the mother and father and increased risk of childhood recurrent abdominal pain⁷² and Lyngsøe et al found associations between maternal depression and higher prevalence of somatic health complains including stomach ache and constipation⁷³. Study IV added to this field by showing that both maternal and paternal minor mental health conditions treated solely in primary care and more severe conditions requiring specialised mental healthcare were associated with increased risk of paediatric FGID diagnosed at hospital settings.

Some of the association between parental mental health conditions and child FGID might be explained by the high comorbidity between gastrointestinal and mental

health problems^{69,117,139} and the fact that mental health problems are frequent in children of parents with mental health conditions¹². Further, increased prevalence of abdominal pain is found in children with high stress levels and a range of stressors, such as disadvantaged socioeconomic conditions, were found associated with functional abdominal pain and constipation^{69,138}. Building on this, the findings of study IV suggest an important role of psychosocial pathways when explaining the association between parental mental health conditions and child FGID.

Hospital diagnoses of FGID can be interpreted as more severe cases of FGID as FGID preferably are treated by GPs and only severe or complicated cases might be referred to hospital assessment. Several elements in the treatment of FGID are considered family interventions, such as education and psychological therapy, involving both child and parent¹⁴⁰. Thus, handling FGID in their children might be demanding for the parents, and maybe even more demanding for parents with mental health conditions, as these can affect cognitive functions^{141–143} and parenting skills²⁵.

As further described in section 1.5.3., it was hypothesised that PCHE participation compared to no participation was associated with a lower risk of a hospital diagnosis of FGID in the overall population and especially in children of parents with mental health conditions. However, the opposite was found; that PCHE participation was associated with an increased risk of FGID hospital diagnosis in the overall population as well as in children of parents with mental health conditions, and the association tended to be stronger for children of parents with mental health conditions. A Danish study examined whether PCHE participation minimised social difference in the use of specialist care outside the hospital system and reported that if the child attended any PCHE, they had the same probability of contact with a specialist regardless of the parent's income¹⁴⁴. They also reported an overall association between PCHE participation and an increased number of contacts with specialist¹⁴⁴. This is in a way comparable to the findings in study IV of increased risks of hospital diagnoses of FGID in the overall population. However, as also noticed by the before mentioned study¹⁴⁴, the effect of PCHEs is poorly examined⁷⁹; also a systematic search in PubMed did not reveal any other comparable studies.

Lykke and colleagues observed PCHEs and performed interviews and concluded that the PCHEs were “*an important platform for examination and dialogue concerning a child's health*”¹⁴⁵. The examination of the physical health and development was well-established, but the parents rarely mentioned their worries about the child's psychosocial health or the mental well-being of their own, and the GPs did not ask. Therefore, the study stated a need for improvement of the assessment of the child's mental health and the family's well-being¹⁴⁵.

General health checks in adults have been examined with little or no effect on finding disease early or preventing disease from developing¹⁴⁶. The health checks lead to increased use of diagnostic and therapeutic interventions that can be harmful as well

as beneficial¹⁴⁶. The reason for lack of effect might be that the GP already identify and intervene when they see the patient for other reasons¹⁴⁶. It may be hypothesised that the same mechanism explains some of the association in this paediatric population; The GP may be more likely to refer the child with FGID to hospital assessment if the child attend to PCHE. Further, the relation and familiarity between GP and child/parent that attend the PCHEs do not impact the likelihood of treatment of the FGID solely at the GP.

To summarise, the effect of the PCHE is poorly studied, and the results of this study regarding PCHE must be interpreted with caution and further examined in future studies.

5.1.6. DISCUSSION ACROSS ALL STUDIES

The results of the four studies support and expand on current knowledge about the vulnerability in children of parents with mental health conditions by showing increased risks of a range of morbidities and increased use of healthcare services throughout early childhood.

A gradient of child health inequalities?

One of the aims of this thesis was to contribute with new knowledge of the impact of different severities of parental mental health conditions on child morbidity.

A dose-response relationship or a gradient between the severity of mental health condition and child morbidity was seen for several outcomes, most evident for maternal exposure. A distinct gradient was seen for the outcomes of 5-minutes Apgar score <7 (study I), inpatient and outpatient contacts (study II).

For other outcomes, a tendency of gradient was seen. For example, the estimate of severe mental health condition was higher than for minor and moderate mental health condition, which yielded similar estimates such as for 5-minutes Apgar score <4 and neonatal hospital admission (study I). The estimates of severe and moderate mental health conditions were similar and higher than for minor mental health conditions such as for out-of-hour contacts and emergency department contacts (study II) and FGID (study IV).

The three severities of mental health conditions yielded similar estimates for a couple of outcomes (GP contacts in study II, and asthma in study III). One explanation might be that minor mental health conditions managed only in primary care may be easily overlooked. In Denmark, pregnant women are offered psychosocial risk assessment in early pregnancy and women with mental health conditions are offered a higher level of care and tailored services¹⁴⁷. Parents with more severe conditions may however be

easier identifiable from hospital records and receive more clinical attention compared to parents with minor mental health conditions.

To sum up, many of the early childhood health outcomes examined in this thesis, seemed to increase with increasing severity of parental, mainly maternal, mental health condition indicating a gradient of child health inequalities. Overall, the results point to a broader public health focus on parent's mental health in general including mental health conditions treated solely at primary care.

Double trouble – double risk

Evidence of a higher share of less socioeconomic advantage in parents with mental health conditions was reported; the share of children with parents with low educational level, low household income and single parents was increasing with increased severity of the mental health condition. Moreover, study III reported an excess risk of asthma in children of parents with both mental health conditions and socioeconomic disadvantaged position corroborating the bidirectional relationship between mental health and socioeconomic position.

These findings emphasise the importance of a focus on the several determinants of child health including factors of the structural, material and psychosocial pathways when prioritising resources and planning intervention to reduce early childhood morbidity.

The role and potential of the GP

The GP is the consistent healthcare professional before, under and after pregnancy. All pregnant women are offered three consultations at the GP during the pregnancy with the purpose of assessing physical and psychosocial risk factors and resources¹⁴⁷. Further, the seven preventive child health examinations during the first five years of life is great opportunity to identify these children. In relation to this thesis, the GPs have a key role in identifying risk factors during pregnancy that may lead to adverse perinatal outcomes (study I), early identification and assessment morbidity during the first year of life (study II), early identification and assessment of childhood asthma (study III) and finally a key role in identifying and assessment childhood functional gastrointestinal disorders (study IV).

Thus, the GPs have the opportunity of an extensive, preventive effort during pregnancy and early childhood. But identifying of these parents and their children might be challenging for the GP. A recent Danish study found that GPs might be reluctant in trusting their gut feelings and misjudging parents on their visual appearance, especially in absence of a doctor-patient relationship¹⁴⁸. Also findings from UK report barriers of identification among GPs¹⁴⁹. Further, handling these children might be challenging. Forty percent of GPs in a Danish study found that their knowledge on the impact of parental depression on the child were poor¹⁵⁰, and an evaluation reported a demand of more focus on mental and social issue by both the

GP and the parents⁷⁸. Further, a Norwegian qualitative study reported that although the GPs knew options of how to support children of parents with poor mental health, the GPs experienced barriers such as lack of time, the child was outside the focus of the consultation and fear of jeopardising the relationship with the parent¹⁵¹. The full potential of the GPs may therefore not seem to be made use of. A need to fulfil this potential of the GP is emphasised by the findings of this thesis. This may include structural changes, such as more time for consultations and PCHEs. Moreover, strengthening of the GPs competences, e.g. communication skills and knowledge of the risks of the children, might be considered¹⁵².

Fathers matter?

For more outcomes of this thesis, no or only sparse association for paternal exposure was found. Poor mental health of the father, independent of mental health of the mother, increased the use of out-of-hour medical service, emergency department, inpatient and outpatient (only for minor and moderate mental health condition) during the first year of the child's life by nine to 26% (Figure 7). As described in section 5.1.3, the results indicated a potentially protective effect of having a 'mentally healthy' parent. Out-of-hour medical service, emergency department and inpatient contacts are in general unplanned healthcare contacts and could reflect acute illness such as infections and injuries. The hypothesis of an association between poor mental health of the father and increased risk of child injuries is supported by a recent Swedish study that found an adjusted RR of 1.27 (95% CI 1.21-1.33) of injuries in children aged 0-1 of fathers with mental illness¹³¹.

Although the association between an increased risk of a FGID diagnosis in children and fathers with mental health conditions were modest, a similar association was reported by Ramchandani et al (adjusted OR of 1.38 (95% CI 1.12-1.71))⁷², which supports the interpretation of the association as an effect.

However, no statistically significant or only a weak association between the father's mental health and perinatal outcomes (study I) or asthma (study III) was found. These findings might be due to the influence of environmental factors such as in utero negative effects on the foetus and maternal lifestyle factors associated with mental health conditions. Further, children of parents with severe mental illness are more likely to co-habit with their mother than father¹⁵³, therefore depending most upon the care of the mother.

Overall, although the association between father's mental health and some outcomes were limited, the impact of the father should not be neglected.

Public health relevance

All four studies reported that poor parental mental health modestly increased risks of most outcomes of child morbidity. From a public health perspective, these findings represent a high burden of disease as the prevalence of children with parents with

mental health conditions is high, ranging from seven percent to 38% in the four studies with different exposure periods. The findings in this thesis of the many parents with continuous mental health conditions through the early years of the child's life (section 4.5. almost three quarters of the mothers with poor mental health 12 months prior to birth are also categorised with poor mental health during early childhood) highlights an issue of public health relevance and emphasises the importance of early detection and intervention.

5.2. METHODOLOGICAL ISSUES

Limitations exist in all research and is important to evaluate as the results of the research should be interpreted in the light of the limitations. In observational studies internal validity, affected by bias and confounding, and external validity, such as generalisation, should always be assessed.

This section will discuss strengths and limitations of the four studies in this thesis.

5.2.1. INTERNAL VALIDITY

Confounding

Confounding is a concern in almost all observational studies; therefore, attention of measured and unmeasured (e.g. residual) confounders is needed. A range of potential confounders were adjusted for, such as parental education, household income, parental cohabitation, country of origin and parental age (section 3.6). However, no information was available on social support/network that may be a confounder in all four studies. In study I, no data was available on pre-pregnancy body mass index that is associated with adverse perinatal outcomes and might be overrepresented in the exposed groups. However, gestational diabetes, which was controlled for, is strongly associated with pre-pregnancy body mass index¹⁵⁴, and was expected to make up for some of this potential unmeasured confounding.

Further, several behavioural factors, such as smoking and diet, can be argued to be confounders as well as mediators of the association between parental mental health and child health outcomes. Information on maternal smoking during pregnancy was available and adjusted for in study I. It would have been interesting to be able to adjust for e.g. parental smoking in study II and III to examine the influence hereof. Further, housing conditions may affect child asthma. However, this information was not available, and not being able to condition on behavioural factors are often a limitation in register-based studies.

Residual confounding due to unknown or unmeasured risk factors might exist in all four studies.

Information problems

In research, information on mental health are often based on self-reported mental symptoms, a single screening of mental health condition and/or a single/few diagnosis. Self-report is associated with recall bias that should not be an issue in this thesis with only register-based information.

By including a broader definition of mental health conditions by severity based on health professional assessment using the nationwide health registers, misclassification due to reporting bias are expected to be reduced. Further, the criteria are closely related to national guidelines and thoroughly described in section 3.4.1.

There may be a risk of misclassification of the used diagnoses from Danish National Patient Register being both regarding misclassification of exposure and outcome. Potential differences in registration practice among hospital departments and over time might exist⁸⁹. Moreover, varying validity of the individual variables have been reported, and only two studies regarding diagnoses used in this thesis were found in a systematic review⁸⁹. A study examining the validity of discharge diagnoses on asthma (ICD-10 DJ45-46 as used in study III) in children aged 6-14 years found positive predictive value of 0.85¹⁵⁵. Further, the positive predictive value of the infant respiratory distress syndrome diagnosis (ICD10 P22.0) has been estimated (used in study I)¹⁵⁶. The overall positive predictive value of the diagnosis was 81%, and higher (89%) for infants born before 37 weeks of gestation¹⁵⁶. Consequently, potential misclassification of these diagnosis should be considered. These potential misclassifications are most likely nondifferential since the classification errors are expected to be the same across groups, and bias due to nondifferential misclassification is predictable in direction toward or beyond the null value¹²¹ leading to an underestimation of the true association.

Moreover, misclassification of exposure within the consensus definition of mental health conditions might exist. Parents who did not seek care for their mental health condition were misclassified as being in the reference group. A study using approximately the same hierarchical levels of mental health care as presented in Figure 4, section 3.4.1. reported that more than half of the study participants with moderate to severe symptoms of depression received no treatment beyond GP assessment/consultation¹⁰². Especially people with abuse are less likely to seek healthcare¹⁵⁷. Further, in Denmark treatment of substance and alcohol abuse are handled by local health centres in the municipalities, and information hereof are not available in any of the included registers. Thus, parents with abuse were misclassified as reference. As these misclassifications were expected to occur independently of the outcomes, this would lead to nondifferential misclassification producing bias toward the null value and consequently lead to an underestimation of the true association.

Parents with moderate and severe conditions, such as depression, treated solely at GP and/or psychologists are further misclassified in the minor category.

The structure and organisation of the Danish healthcare system with GPs as gatekeepers to the secondary specialised healthcare provides an opportunity to examine different severities of mental health conditions. One study reported that study participant with more severe symptoms were met with a higher level of care though 10% with moderate to severe symptoms of depression had no mental healthcare contact at all¹⁰². Thus, the definition of the different severities of mental health conditions are related to uncertainties and the underneath lined issues, and the interpretation of the results of this thesis should be in the light of these. Factors potentially associated with nondifferential misclassification might include, among others, following:

First, characteristics of the GP: With approximately 3500 GPs in Denmark, the GPs may have somewhat different competencies and experiences. GPs with competences in talk therapy and more experience with psychiatric treatment might be less likely to refer the parent to psychiatrist or psychiatric hospital. Moreover, the frequency of errors in the coding of specific services by the GP is not known as no validity studies have been reported. The definition of some codes is vague (e.g. talk therapy) and subject to variation between the providers⁹².

Secondly, characteristics of the parent: In Denmark, there is 60% out-of-pocket co-payment for therapy at psychologists after referral from GP¹¹². Therefore, some GPs might be more likely to refer patients with less financial resources to psychiatrist or psychiatric hospital where there is no co-payment. Third, characteristics of municipality/geography: The distance to psychiatric hospital and the number of practising/office-based psychiatrists and psychologists might also affect the likelihood of referral of the GP along with the implementation of shared care. The issue of distance to hospital and number of office-based specialists might also affect the likelihood of the GP referring the child to hospital assessment of FGID as described in study IV. This issue was handled in this study by controlling for municipality. These factors will most likely lead to misclassification between the exposure categories.

Selection problems

The Danish registers are in general considered valid in terms of completeness, registration processes and accuracy^{87,89,91}. The use of an entire population as cohort minimises selection bias and loss to follow-up and maximises external validity^{89,158}.

However, information on stillborn infants was not available as they are not registered at birth⁹⁷. Since stillbirths are more prevalent among women with poor mental health⁵⁴, not including stillborn infants might lead to selection bias, especially in study

I, and lead to an underestimation of the true association. Further, children whose parents did not live in Denmark at some time points during the exposure period were excluded as the exposure status could not be ascertained. If these children differed from the study population, e.g. if their parents more often had mental health conditions, this could lead to selection bias with an underestimation of the true value.

Missing values

Missing observations of the covariates were seen in all four studies; for all covariates less than ten percent except household income used solely in study II.

All adjusted analyses were based on complete case. In study II, it was tested whether a different approach affected the results by making an analysis, where the missing data on income, parental education and paternal age were categorised. This did not change the estimates noteworthy (data not shown). Imputation was not found suitable for the covariates since these missing data did not seem to be random.

5.2.2. EXTERNAL VALIDITY

All four studies included all children in Denmark born alive in the respective study periods, thus the entire population. Therefore, the results are generalisable to Danish settings and settings with healthcare systems similar to the Danish, such as the Nordic countries as well as United Kingdom and the Netherlands. Further, the overall findings of associations between parental mental health and child health might have broad applicability.

In summary, several limitations and strengths of the studies in this thesis must be considered when interpreting the results. Overall, the studies have high internal and external validity and the results must be considered trustworthy and applicable to the real world.

CHAPTER 6. CONCLUSION

From the very beginning of life and throughout early childhood this thesis reported increased risks of a wide range of adverse health outcomes in children of parents with mental health conditions compared to children of parents without mental health conditions. Increased risks were found for both minor, moderate and severe mental health conditions. For more outcomes, the findings indicated a gradient of health inequalities in early childhood with increasing severity of parental mental health condition. Overall, the results point to a broader public health focus on parent's mental health in general including mental health conditions treated solely at primary care.

Although the effect of mental health of the mother was strongest, an independent risk in children of fathers with poor mental health was found. Results indicated a potentially protective effect of having a 'mentally healthy' parent for some child health outcomes. Therefore, the father's mental health should not be neglected.

This thesis reported a gradient of disadvantaged socioeconomic conditions with higher shares of parents with lower educational level and single parents with increasing severity of mental health conditions. This means that parental mental health conditions along with other risk factors of adverse health outcomes in the children often are cooccurring such that these families are facing several difficulties. An extra high risk of asthma was found in children exposed to both parental mental health conditions and socioeconomic disadvantage suggesting an excess hazard for these children. This highlight a group of children (and parents) that might particularly benefit from a preventive intervention.

An intervention that might reduce inequalities in child health is the preventive child health examinations at GP. This thesis reported that preventive child health examination participation was associated with an increased risk of a hospital diagnosis of functional gastrointestinal disorder, a condition preferably treated at GP.

CHAPTER 7. IMPLICATIONS

The finding of this thesis could be relevant for a broad range of clinical health professionals in primary as well as secondary healthcare such as GPs, paediatricians, psychiatrists, midwives and health nurses. The results apply to health professionals treating the parents as well as the children. They should be aware that not only severe mental health conditions, such as schizophrenia, bipolar disorder and moderate-severe depression in parents constitutes a risk of adverse child health, but also less severe mental health conditions only treated at primary care by GPs and/or psychologists. The findings of this thesis emphasise the relevance of – as already proposed by the Danish Medical Association¹⁵⁹ – an obligation for physicians, including GPs and psychiatrists, to ask patients, potential mothers as well as fathers, with mental health conditions whether they have children. However, identification should be followed by action and sharing the knowledge of the children at risk between relevant actors is important.

Increased awareness lead to the need of effective communication opportunities such as the psychiatrist treating the parent easily can communicate with the health professionals treating the child or social worker that can support the family. A Danish focus group examination of GPs reported that handling the issues of vulnerable patients required a good collaboration with the other players in the healthcare system, which often was experienced as insufficient, difficult and with unclear division of responsibilities¹²⁹. Further, the social distribution of parental mental health conditions highlights the importance of a broader focus of the whole family and its resources and challenges and emphasising the importance of collaboration between different sectors, e.g. the health and social sector, as well as collaboration between different actors within the healthcare system, for example GPs and psychiatrists or paediatricians. Overall, this calls for strengthening of the intersectional and cross-sectional collaboration.

7.1. FUTURE RESEARCH

Given the limitations of this thesis, validation of the definition of mental health conditions could be considered for future research. Especially the minor category including information from general practice could preferably be examined to get insights of the amount of potential misclassification.

It would be interesting and useful knowledge to examine the impact of the GP and the preventive child health examinations. For example, recently a new agreement between PLO (Organisation of Practising Physician) and Danish Regions were made¹⁶⁰. Some of the main points in the agreement are an outreach effort regarding preventive child

health examinations and, when needed, consultation for children/families with special challenges¹⁶⁰. The purpose of the initiative is to reduce inequality in health by early detection of somatic illness and thus prevent severe complications¹⁶⁰. However, it is unknown whether this outreach effort regarding the preventive child health examinations reduce inequality in health. Although this initiative may be an opportunity to investigate this question, e.g. by cluster randomisation, an evaluation or research in relation to this new initiative has not been prioritised. The influence of preventive child health examinations seems to suffer from the so-called inverse evidence law, whereby there is least research on the interventions with the greatest potential to improve health²⁶.

The findings of the social distribution of poor mental health should lead to a focus on both factors, mental health and socioeconomic circumstances, in studies examining either to limit the risk of residual confounding. Otherwise, studies examining associations between e.g. perinatal health and educational level¹⁶¹ might to some extent, yet unknown, be confounded by poor mental health.

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SUPPLEMENTARY TABLE

Supplementary table 1 of exposure overlap between the four studies					
N individuals included in all four studies = 678,537					
Maternal exposure groups					Overall study population
	Study I N (%)	Study II N (%)	Study III N (%)	Study IV N (%)	Percentage of the original study population
Study I	40,482	40,482 (100.0)	40,482 (100.0)	30,076 (74.3)	71.3
Study II	40,482 (36.7)	110,445	88,993 (80.6)	68,855 (62.3)	70.4
Study III	40,482 (24.4)	88,993 (53.7)	165,832	124,865 (75.3)	73.3
Study IV	30,076 (15.7)	68,855 (36.0)	124,865 (65.3)	191,266	90.4
Paternal exposure groups					Overall study population
	Study I N (%)	Study II N (%)	Study III N (%)	Study IV N (%)	Percentage of the original study population
Study I	30,472	30,472 (100.0)	30,472 (100.0)	21,924 (71.9)	71.3
Study II	30,472 (41.6)	73,255	58,588 (80.0)	41,024 (56.0)	70.4
Study III	30,472 (29.5)	58,588 (56.7)	103,344	75,622 (73.2)	73.3
Study IV	21,924 (18.3)	41,024 (34.2)	75,622 (63.0)	119,973	90.4

APPENDICES A-D

Appendix A: Article of study I – see separate file

Appendix B: Article of study II – see separate file

Appendix C: Article of study III – see separate file

Appendix D: Article of study IV – see separate file

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