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# Children and Adolescents with Parental Mental Illness (CAPRI) – Prevalence, Physical Health, and Social Outcomes



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# CHILDREN AND ADOLESCENTS WITH PARENTAL MENTAL ILLNESS (CAPRI) – PREVALENCE, PHYSICAL HEALTH, AND SOCIAL OUTCOMES

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

**Alicia Nevriana**

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To Dr Nisyawati and Dr Abinawanto

The first Doctors of Philosophy I've ever met in my life

*“Sesungguhnya sesudah kesulitan ada kemudahan.”*

*(Q.S. 94:6)*



## POPULAR SCIENCE SUMMARY

About 1 billion people around the world are affected by mental health problems every year. A considerable proportion among them are parents with children under 18 years. Having mental health problems might affect the lives of affected persons, as well as the lives of families and people around them. When the parents have a mental illness, their children are amongst the most affected and might, therefore, need support. However, there has been little knowledge about the numbers of children living with mentally ill parents in Sweden and on the health and social outcomes of these children. Therefore, this thesis took advantage of the Swedish health and administrative registers to examine the prevalence, health, and social outcomes of children and adolescents with parental mental illness.

We found that approximately one in ten children aged 0-17 years in Sweden had at least one parent with a mental illness severe enough to be treated within psychiatric care. We showed that these children were exposed to broad socioeconomic adversity. For example, they were considerably more likely to live in households in the lowest income group or have unemployed parents. Exposure to both socioeconomic adversity and parental mental illness might synergistically and negatively impact the health and social outcomes of these children, but this had been less studied.

One of our studies on health outcomes showed that among children aged 0-17 years in Sweden, those with at least one mentally ill parent had a 6-30% increased risk for injuries compared to children without mentally ill parents and the risk was highest during the child's first years of life (30%). The risk was slightly higher if it was the mother than the father who had the mental illness, and also for rarer types of injuries (e.g., violence-related) compared to more common types of injuries (e.g., falls). The risk was also slightly higher if the parents received common mental disorders diagnoses (e.g., depression or anxiety) compared to if the parents received more serious diagnoses, e.g., psychosis.

In another study, we showed that children with parental mental illness were overall slightly more likely (5%) to receive a diagnosis of autoimmune disease, compared to children without parental mental illness. However, there were differences by type of parental mental illness and autoimmune disease. While the majority of parental psychiatric diagnoses appear not to increase the risk of autoimmune disease in children, we found that children of mothers with eating disorders (e.g., anorexia or bulimia) or depression were 10-40% more likely to be diagnosed with type 1 diabetes. Children of parents with depression or anxiety were also more likely to be diagnosed with psoriasis or juvenile arthritis. On the other hand, children of mothers with psychosis were up to 30% less likely to be diagnosed with coeliac disease.

Our study on parental mental illness and risk of cancer in children, which included large population-based cohorts from both Sweden and England, did not show any significant associations between mental disorders in parents and the risk of cancer in children. Yet, we found that children with maternal psychosis appeared to be 25% less likely to be diagnosed



with cancer compared to children without maternal psychosis. This finding might need replication in larger studies.

Having multiple adversities, as this thesis showed is often the case for families with mentally ill parents, might make it challenging for the families to provide an environment that could support the children. The last study included in this thesis showed that, overall, children with parental mental illness were four times more likely to be placed in out-of-home care, compared to other children without parental mental illness in Sweden. They were more likely to be placed when they were very young (0-1 years) and when the parents received diagnoses of intellectual disability, alcohol/drug misuse, or schizophrenia. Further, our results revealed that the risk was markedly increased if the children also lived in families that experience socioeconomic adversity. For instance, if the children also lived in the household within the lowest income group, they would be up to nine times more likely to be placed in care outside of their homes.

Overall, this doctoral thesis showed that a considerable proportion of children in Sweden have at least one parent with mental illness. These children were more likely to experience a range of adversity, both when it comes to physical health and social conditions, compared to other children. Therefore, this thesis calls for improved support to families where the parents have a mental illness in order to ensure the well-being of all children.

# POPULÄRVETENSKAPLIG SAMMANFATTNING

Cirka 1 miljard människor runt om i världen drabbas av psykisk ohälsa varje år. En betydande andel av dem är föräldrar med barn under 18 år. Att drabbas av psykisk ohälsa kan påverka den enskildes liv, familjens liv, och andra i omgivningen. När föräldrar drabbas av psykisk ohälsa är deras barn bland de mest påverkade och kan därför behöva stöd. Det finns dock begränsad kunskap om hur många barn som har föräldrar med psykisk ohälsa i Sverige samt deras hälsa och sociala förhållande. Denna avhandling baserades på svenska hälso- och administrativa databaser för att undersöka prevalens, fysisk hälsa, samt sociala förhållande hos barn och ungdomar som har föräldrar med psykisk ohälsa.

Ungefär vart tionde barn (0–17 år) i Sverige hade minst en förälder som diagnostiserats med psykisk ohälsa inom specialistvård under åren 2006–2016. Dessa barn var utsatta för flera socioekonomiska svårigheter. Till exempel hade de högre sannolikhet att leva i hushåll i den lägsta inkomstgruppen eller att ha arbetslösa föräldrar. Exponering för både socioekonomiska svårigheter och föräldrars psykiska ohälsa kan synergistiskt och negativt påverka barnens hälsomässiga och sociala utfall, men detta har inte studerats i någon större utsträckning.

En av våra studier visade att barn som hade åtminstone en förälder med psykisk ohälsa löpte 6–30 % högre risk för skador och risken var högst under barnets första levnadsår (30 %). Risken var något högre om det var mammorna som drabbades (jämfört med papporna), och för mer sällsynta typer av skador (till exempel våldsrelaterade) jämfört med vanligare skador (till exempel fallskador). Risken var också något högre om föräldrarna fick relativt vanliga psykiska sjukdomar (till exempel depression eller ångest) jämfört med om föräldrarna fick allvarligare diagnoser, till exempel psykos.

I en annan studie visade vi att barn som hade föräldrar med psykisk ohälsa hade något högre risk (5 %) att diagnostiseras med autoimmuna sjukdomar. Det fanns dock skillnader mellan olika typer av psykiatriska och autoimmuna sjukdomar. Majoriteten av föräldrarnas psykiatriska diagnoser verkade inte öka risken för autoimmuna sjukdomar hos barn. Vi fann dock att barn till mammor med ätstörningar (till exempel anorexi eller bulimi) eller depression löpte 10–40 % högre risk att få en typ 1 diabetes-diagnos. Barn till föräldrar med depression eller ångest hade också högre sannolikhet att diagnostiseras med psoriasis eller juvenil idiopatisk artrit. Å andra sidan hade barn till mammor med psykos upp till 30 % lägre risk att få celiakidiagnos.

Vår studie om föräldrars psykiska ohälsa och risk för cancer hos barn, som omfattade stora befolkningsbaserade kohorter från både Sverige och England, visade inga signifikanta samband mellan psykiatriska sjukdomar hos föräldrar och risken för cancer hos barn. Vi fann dock att barn vars mammor hade psykos verkade ha 25 % lägre risk att få cancerdiagnos. Detta kan behöva replikeras i fler och större studier.

Att ha flera motgångar, vilket denna avhandling har visat ofta är fallet för familjer där åtminstone en förälder drabbas av psykisk ohälsa, kan göra det utmanande för familjerna att

tillhandahålla en miljö som kan stödja barnen. Den sista studien i denna avhandling visade att barn som hade föräldrar med psykisk ohälsa hade fyra gånger högre sannolikhet att placeras utanför det egna hemmet, jämfört med andra barn i Sverige, särskilt när de var mycket unga (0–1 år). De hade också högre sannolikhet att bli placerade när föräldrarna diagnostiserats med intellektuell funktionsnedsättning, alkohol-/drogmissbruk eller schizofreni. Risken ökade markant om barnen också levde i familjer som hade socioekonomiska svårigheter. Om barnen till exempel dessutom bodde i hushåll i den lägsta inkomstgruppen, hade de upp till nio gånger högre risk att placeras utanför sina hem.

Sammantaget visade denna doktorsavhandling att en betydande andel av barnen i Sverige har minst en förälder med psykisk ohälsa. Dessa barn hade högre sannolikhet att uppleva en rad motgångar, både när det gäller fysisk hälsa och sociala förhållanden, jämfört med andra barn. Mot bakgrund av detta efterlyser denna avhandling förbättrat stöd till familjer där föräldrarna har psykisk ohälsa för att säkerställa alla barns välmående.

## RINGKASAN SAINS POPULER

Sekitar 1 miliar orang di dunia mengalami masalah kesehatan mental setiap tahunnya. Banyak di antaranya merupakan orang tua dengan anak di bawah usia 18 tahun. Mengalami masalah kesehatan mental tidak hanya dapat mempengaruhi kehidupan kita, tetapi juga kehidupan keluarga dan orang-orang di sekitar kita. Ketika orang tua mengalami masalah kesehatan mental, maka ada kemungkinan hal tersebut akan mempengaruhi anak-anak mereka, sehingga mereka pun membutuhkan dukungan. Meski demikian, tidak banyak yang diketahui mengenai berapa jumlah anak-anak yang memiliki orang tua dengan masalah kesehatan mental di Swedia. Kita juga tidak banyak mengetahui mengenai kondisi kesehatan dan sosial dari anak-anak tersebut. Oleh karena itu, penelitian-penelitian di dalam disertasi ini bertujuan untuk mencari tahu berapa banyak anak-anak yang memiliki orang tua dengan masalah kesehatan mental di Swedia, serta bagaimana kondisi kesehatan dan sosial mereka, dengan memanfaatkan berbagai register kesehatan dan administrasi di Swedia.

Kami menemukan bahwa sekitar satu dari sepuluh anak berusia 0-17 tahun di Swedia memiliki setidaknya satu orang tua yang didiagnosis dan mendapat perawatan untuk penyakit mental di fasilitas pelayanan kesehatan sekunder. Anak-anak ini pun biasanya tinggal di keluarga yang juga mengalami kesulitan sosial ekonomi lain, misalnya, tinggal di keluarga dengan kelompok penghasilan terendah atau memiliki orang tua yang tidak memiliki pekerjaan. Kesulitan sosial ekonomi dan kondisi kesehatan orang tua tersebut mungkin saja dapat bersinergi dan berdampak negatif pada kesehatan dan kondisi sosial lainnya dari anak-anak ini, tetapi hal ini belum banyak diketahui.

Salah satu penelitian kami mengenai kesehatan anak-anak tersebut menunjukkan bahwa mereka memiliki risiko cedera hingga 30% lebih tinggi, terutama pada usia 0-1 tahun, dibandingkan dengan anak-anak yang orang tuanya tidak didiagnosis dengan penyakit mental. Risikonya sedikit lebih tinggi jika ibunya yang didiagnosis dengan penyakit tersebut, ketimbang ayahnya. Risikonya juga sedikit lebih tinggi untuk jenis cedera yang lebih jarang (misalnya cedera akibat kekerasan) dibandingkan dengan jenis cedera yang lebih umum (misalnya karena jatuh). Risikonya pun sedikit lebih tinggi jika orang tuanya menerima diagnosis penyakit mental yang lebih umum (misalnya depresi atau gangguan kecemasan), dibandingkan dengan jika orang tua menerima diagnosis yang lebih serius, misalnya, psikosis.

Pada penelitian lain, kami menemukan bahwa anak-anak yang orang tuanya memiliki penyakit mental secara keseluruhan memiliki risiko sedikit lebih tinggi (5%) untuk didiagnosis dengan penyakit autoimun. Meski demikian, terdapat perbedaan risiko berdasarkan kombinasi diagnosis penyakit mental pada orang tua dan penyakit autoimun pada anak-anak. Sebagian besar diagnosis penyakit mental pada orang tua tidak berhubungan dengan peningkatan risiko penyakit autoimun pada anak-anak. Meski demikian, kami menemukan bahwa anak-anak dari ibu yang memiliki gangguan makan (misalnya anoreksia atau bulimia) atau depresi memiliki risiko 10-40% lebih tinggi untuk didiagnosis dengan diabetes tipe 1. Anak-anak dari orang tua yang mengalami depresi atau gangguan kecemasan

juga lebih sering didiagnosis dengan psoriasis atau penyakit artritis pada anak. Di sisi lain, anak-anak dari ibu yang memiliki psikosis memiliki risiko 30% lebih rendah untuk didiagnosis dengan penyakit seliak.

Untuk mengetahui risiko kanker pada anak-anak yang orang tuanya mengalami penyakit mental, kami menggabungkan juga data yang kami miliki dari Swedia dengan data dari Inggris. Hasil dari penelitian ini tidak menunjukkan adanya peningkatan risiko yang signifikan untuk kanker. Di sisi lain, penelitian ini menunjukkan bahwa anak-anak yang ibunya mengalami psikosis memiliki risiko 25% lebih kecil untuk didiagnosis dengan kanker. Temuan ini mungkin perlu direplikasi di studi yang lebih besar.

Mengalami kesulitan sosial ekonomi, seperti yang sering dialami di keluarga yang orang tuanya mengalami masalah kesehatan mental, mungkin akan menyulitkan keluarga dalam menyediakan lingkungan yang dapat mendukung tumbuh kembang anak. Penelitian terakhir pada disertasi ini menunjukkan bahwa, secara keseluruhan, anak-anak yang orang tuanya mengalami penyakit mental, memiliki risiko empat kali lebih besar untuk ditempatkan oleh dinas sosial di keluarga lain atau fasilitas khusus yang terpisah dari orang tuanya. Penempatan seperti ini biasanya lebih sering terjadi ketika mereka berusia sangat muda (0-1 tahun) atau ketika orang tuanya memiliki diagnosis disabilitas intelektual, penyalahgunaan alkohol/narkoba, atau skizofrenia. Penelitian ini juga menunjukkan bahwa risiko untuk penempatan semacam ini meningkat tajam jika anak-anak tersebut juga tinggal di keluarga yang mengalami kesulitan sosial ekonomi. Misalnya, risiko yang tadinya empat kali lebih besar, bisa menjadi sembilan kali lebih besar jika mereka juga tinggal di keluarga berpenghasilan rendah.

Secara keseluruhan, disertasi ini menunjukkan bahwa sebagian anak-anak di Swedia memiliki setidaknya satu orang tua yang mengalami penyakit mental. Anak-anak ini cenderung lebih sering mengalami berbagai kesulitan, baik dalam hal kesehatan maupun kondisi sosial, dibandingkan dengan anak-anak lain. Oleh karena itu, perlu adanya dukungan yang mencukupi bagi keluarga yang orang tuanya mengalami masalah kesehatan mental agar kesejahteraan anak-anaknya dapat terpenuhi.

## ΠΕΡΙΛΗΨΗ

Περίπου 1 δισεκατομμύριο άνθρωποι σε όλο τον κόσμο πλήττονται από προβλήματα ψυχικής υγείας κάθε χρόνο. Ένα σημαντικό ποσοστό μεταξύ αυτών είναι γονείς με παιδιά κάτω των 18 ετών. Τα προβλήματα ψυχικής υγείας μπορεί να επηρεάσουν τη ζωή των πασχόντων καθώς και αυτή των οικογενειών και των γύρω τους. Όταν οι γονείς πάσχουν από μια ψυχική ασθένεια τα παιδιά τους επηρεάζονται περισσότερο και ως εκ τούτου μπορεί να χρειάζονται υποστήριξη. Ωστόσο, γνωρίζουμε ελάχιστα σχετικά με τον αριθμό των παιδιών που ζουν με γονείς με ψυχικές νόσους στη Σουηδία και αλλού, καθώς και για την υγεία και την κοινωνική ευημερία αυτών των παιδιών. Ως εκ τούτου, η διατριβή αυτή αξιοποίησε σουηδικές υγειονομικές και διοικητικές βάσεις δεδομένων για να εξετάσει τον επιπολασμό των παιδιών με γονείς με ψυχικές παθήσεις καθώς και τα προβλήματα υγείας και κοινωνικής ευημερίας που αντιμετωπίζουν τα παιδιά αυτά.

Διαπιστώσαμε ότι περίπου ένα στα δέκα παιδιά ηλικίας 0-17 ετών στη Σουηδία είχε τουλάχιστον έναν γονέα με ψυχική ασθένεια αρκετά σοβαρή ώστε να χρειάζεται ψυχιατρική φροντίδα. Δείξαμε επίσης ότι αυτά τα παιδιά εκτέθηκαν σε μεγάλες κοινωνικοοικονομικές αντιξοότητες. Για παράδειγμα, ήταν πολύ πιο πιθανό αυτά τα παιδιά να προέρχονται από οικογένειες με χαμηλό εισόδημα ή οι γονείς τους να είναι άνεργοι. Η έκθεση σε κοινωνικοοικονομικές αντιξοότητες και γονικές ψυχικές παθήσεις μπορεί να επηρεάσει συνεργιστικά και αρνητικά την υγεία και κοινωνική ευημερία αυτών των παιδιών. Τα ευρήματα όμως στη βιβλιογραφία είναι ελάχιστα. Ως αποτέλεσμα, οι επόμενες μελέτες μας εξέτασαν την πιθανότητα για τραυματισμούς, αυτοάνοσα νοσήματα και παιδικό καρκίνο, όπως και την ανάληψη της φροντίδας των παιδιών με γονείς οι οποίοι πάσχουν από ψυχικά νοσήματα από τις υπηρεσίες γονικής μέριμνας.

Η πρώτη μελέτη όσον αφορά τα προβλήματα σωματικής υγείας έδειξε ότι μεταξύ των παιδιών ηλικίας 0-17 ετών στη Σουηδία, εκείνα με τουλάχιστον ένα γονέα με ψυχική νόσο είχαν κατά 6-30% αυξημένο κίνδυνο τραυματισμών σε σύγκριση με άλλα παιδιά, με τον κίνδυνο να ήταν ψηλότερος ειδικά κατά το πρώτο έτος της ζωής τους (30%). Ο κίνδυνος ήταν επίσης ελαφρώς υψηλότερος εάν η μητέρα αντί ο πατέρας πάσχει από κάποια ψυχιατρική νόσο καθώς και για σπανιότερους τύπους τραυματισμών όπως αυτοί που σχετίζονται με βία σε σύγκριση με πιο συνηθισμένους τύπους τραυματισμών όπως οι πτώσεις. Ο κίνδυνος ήταν επίσης ελαφρώς υψηλότερος εάν οι γονείς πάσχουν από κοινές ψυχικές διαταραχές όπως π.χ. κατάθλιψη ή άγχος σε σύγκριση με το εάν οι γονείς έχουν διαγνωστεί με πιο σοβαρές νόσους όπως οι ψυχωτικές διαταραχές.

Σε μια άλλη μελέτη, δείξαμε ότι τα παιδιά με γονείς με που έπασχαν από κάποια ψυχική νόσο είχαν συνολικά κατά 5% περισσότερες πιθανότητες να διαγνωστούν με αυτοάνοση νόσο σε σύγκριση με άλλα παιδιά. Τα αποτελέσματα όμως διαφέρουν με βάση τον τύπο της ψυχικής ασθένειας από την οποία πάσχουν οι γονείς και την αυτοάνοση νόσο στα παιδιά. Ενώ η πλειονότητα των ψυχιατρικών διαγνώσεων στους γονείς φαίνεται να μην αυξάνει τον κίνδυνο αυτοάνοσης νόσου στα παιδιά, διαπιστώσαμε ότι τα παιδιά με μητέρες με διατροφικές διαταραχές (π.χ. ανορεξία ή βουλιμία) ή κατάθλιψη είχαν 10-40% περισσότερες

πιθανότητες να διαγνωστούν με διαβήτη τύπου 1. Τα παιδιά με γονείς που πάσχουν από κατάθλιψη ή άγχος είχαν επίσης περισσότερες πιθανότητες να διαγνωστούν με ψωρίαση ή νεανική ιδιοπαθή αρθρίτιδα. Αντίθετα, τα παιδιά με μητέρες με ψύχωση είχαν έως και 30% λιγότερες πιθανότητες να διαγνωστούν με κοιλιοκάκη.

Η μελέτη μας για τη συσχέτιση γονικής ψυχικής ασθένειας και καρκίνου στα παιδιά η οποία ανέλυσε μεγάλες ομάδες πληθυσμού τόσο από τη Σουηδία όσο και από την Αγγλία δεν έδειξε κάποια σημαντική συσχέτιση μεταξύ των δύο ομάδων διαταραχών. Ωστόσο, διαπιστώσαμε ότι τα παιδιά με μητέρες που πάσχουν από ψυχωτικές διαταραχές φαίνεται να έχουν 25% λιγότερες πιθανότητες να διαγνωστούν με κάποιο παιδικό καρκίνο σε σύγκριση με άλλα παιδιά. Αυτό το εύρημα πρέπει να επαληθευτεί σε ακόμα μεγαλύτερες μελέτες.

Η διατριβή αυτή έδειξε ότι κοινωνικές αντιξοότητες παρουσιάζονται συχνά σε οικογένειες όπου οι γονείς πάσχουν από ψυχικά νοσήματα και αυτό ίσως να δυσχεραίνει αυτές τις οικογένειες να παρέχουν ένα υποστηρικτικό περιβάλλον στα παιδιά τους. Η τελευταία μελέτη που συμπεριλαμβάνεται στη διατριβή αυτή έδειξε ότι τα παιδιά με γονείς με κάποια ψυχική νόσο είχαν τέσσερις φορές περισσότερες πιθανότητες να μετακινηθούν από τις υπηρεσίες γονικής μέριμνας εκτός γονικής εστίας σε σύγκριση με άλλα παιδιά στη Σουηδία. Περισσότερες πιθανότητες για επέμβαση των υπηρεσιών κοινωνικής ευημερίας υπάρχουν όταν τα παιδιά είναι πολύ μικρά σε ηλικία (0-1 ετών) ή οι γονείς πάσχουν από διανοητικές αναπηρίες ή σχιζοφρένεια, ή κάνουν κατάχρηση αλκοόλ ή ναρκωτικών. Επιπλέον, τα αποτελέσματά μας έδειξαν ότι ο κίνδυνος ήταν σημαντικά αυξημένος εάν τα παιδιά προέρχονταν από οικογένειες που αντιμετωπίζουν κοινωνικοοικονομικές αντιξοότητες. Για παράδειγμα, παιδιά από οικογένειες με χαμηλότερο εισόδημα είχαν έως και εννέα φορές περισσότερες πιθανότητες να τεθούν υπό την φροντίδα των υπηρεσιών κοινωνικής ευημερίας της χώρας.

Συνολικά, αυτή η διδακτορική διατριβή έδειξε ότι ένα σημαντικό ποσοστό παιδιών στη Σουηδία έχουν τουλάχιστον έναν γονέα ο οποίος πάσχει από κάποια ψυχική νόσο. Τα παιδιά αυτά ήταν πιο πιθανό να βιώσουν μια σειρά από αντιξοότητες, τόσο όσον αφορά τη σωματική τους υγεία όσο και τις συνθήκες διαβίωσης και ευημερίας τους. Ως εκ τούτου, τα αποτελέσματα αυτής της διατριβής τονίζουν την ανάγκη για βελτιωμένη υποστήριξη των οικογενειών όπου οι γονείς πάσχουν από κάποια ψυχική νόσο προκειμένου να διασφαλιστεί η ευημερία αυτών των παιδιών.

## ABSTRACT

Children and adolescents whose parents have mental illness (CAPRI) are a potentially vulnerable group. Previous studies showed that they are more likely to experience adverse mental health and social outcomes. However, studies investigating their physical health outcomes are scarce. Additionally, reliable estimates on the size of this group and their living conditions in contemporary Sweden is lacking. My thesis aimed to establish the prevalence of CAPRI in Sweden and to deepen our understanding of their physical health and living conditions. Five individual studies were conducted using linkage from various Swedish national registers. One of the studies was also conducted using data from English registers.

In Study I, we estimated the prevalence of children and adolescents up to age 18 with parental mental illness in Sweden and determined the associations with various socioeconomic adversity. We found that around 9.5% of children had at least one parent with mental illness diagnosed within secondary care. The prevalence increased throughout the age and calendar year. These children were also more likely to experience a range of socioeconomic adversity, including having unemployed parents, being in a household that received social welfare benefits, or a household with the lowest income quintile.

In Study II, we determined the associations between parental mental illness and the risk of childhood injury. We found that, overall, CAPRI had a higher risk of injuries compared to children without parental mental illness, especially during the first years of life. The increase in risk was slightly higher for children exposed to maternal, compared to paternal mental illness, and for rarer types of injuries (e.g., violence-related injuries) compared to more common types of injuries, such as falls. All types of parental mental illness were associated with higher risk, although the risk increase was slightly higher for more common mental disorders (e.g., depression and anxiety) compared to more serious mental illness (e.g., psychosis).

In Study III, we determined the associations between parental mental illness and the risk of autoimmune diseases among the children. Parental mental illness was associated with a slight increase in the risk of autoimmune diseases in the offspring. However, the detailed picture was slightly more complicated. The highest risk was observed for type 1 diabetes among children exposed to maternal eating disorders. Additionally, exposure to parental common mental disorders was associated with a higher risk of juvenile arthritis, psoriasis, and type 1 diabetes. On the other hand, exposure to maternal psychosis and paternal alcohol/drug misuse was associated with a lower risk of coeliac disease and inflammatory bowel disease, respectively.

In Study IV, we determined the associations between parental mental illness and the risk of childhood cancer, which is a relatively rare outcome. To increase statistical power, we pooled the estimates from Swedish and English national cohorts. Overall, we did not find enough evidence on the risk of cancer among CAPRI. However, results showed that maternal (but not paternal) psychosis was associated with a 25% reduced risk of childhood cancer, although



confidence intervals for this estimation included the one and therefore this finding needs replication in larger studies. We also found borderline evidence of an increased risk associated with maternal alcohol/drug misuse, but no evidence of a change in risk associated with other types of parental mental illness.

In Study V, we determined whether parental mental illness affected the likelihood of children being placed in out-of-home care and identified which factors might modify such likelihood. We found that CAPRI were more likely to be placed into out-of-home care, especially during the first years of life, compared to children without parental mental illness. While all types of mental illness diagnoses were associated with higher risk, the risk was particularly higher if the parents had a diagnosis of intellectual disability, alcohol/drug misuse, or non-affective psychosis, and if it was the mother who received the diagnosis compared to the father. CAPRI who also lived in lower socioeconomic positions were a subset with a particularly high likelihood of being placed in care outside of their homes.

Overall, these findings showed that CAPRI are common in the contemporary Swedish population. They are more likely to experience adverse physical health outcomes, such as injuries and certain types of autoimmune diseases, but not cancer. They are also more likely to experience poor social outcomes, including socioeconomic adversity and being placed in out-of-home care. This information has important implications for services and public health. We need to maintain awareness of the circumstances in which children live and understand how best to support them and their families if we are to ensure their well-being and improve their life outcomes.

Keywords: mental disorders, wounds and injuries, accidents, autoimmune diseases, neoplasms, foster home care, prevalence, social class, socioeconomic factors, adversity

## LIST OF SCIENTIFIC PAPERS

- I. Pierce M, Abel KM, Muwonge J, Wicks S, **Nevriana A**, Hope H, Dalman C, Kosidou K. Prevalence of parental mental illness and association with socioeconomic adversity among children in Sweden between 2006 and 2016: a population-based cohort study. *Lancet Public Heal.* 2020 Nov 1;5(11):e583–91.
- II. **Nevriana A**, Pierce M, Dalman C, Wicks S, Hasselberg M, Hope H, Abel KM, Kosidou K. Association between maternal and paternal mental illness and risk of injuries in children and adolescents: nationwide register based cohort study in Sweden. *BMJ.* 2020 Apr 8;369:m853
- III. **Nevriana A**, Pierce M, Abel KM, Rossides M, Wicks S, Dalman C, Kosidou K. Association between parental mental illness and autoimmune diseases in the offspring – a nationwide register based cohort study in Sweden. [Submitted]
- IV. **Nevriana A**, Osam CS, Kosidou K, Hope H, Ashcroft DM, Wicks S, Dalman C, Abel KM, Pierce M. Parental mental illness and the risk of offspring cancer in childhood: a pooled meta-analysis of English and Swedish national cohorts. [Submitted]
- V. **Nevriana A**, Kosidou K, Hope H, Wicks S, Dalman C, Pierce M, Abel KM. Risk and modifying factors for out-of-home care placement among children and adolescents with parental mental illness – a population-based cohort study in Sweden. [Manuscript]



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## LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ASD	Autism Spectrum Disorder
CAPRI	Children and Adolescents with PaRental mental Illness
CPRD	Clinical Practice Research Datalink
CI	Confidence Interval
CrI	Credible Interval
GP	General Practitioner
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases
IMD	Index of Multiple Deprivation
JIA	Juvenile Idiopathic Arthritis
LISA	<i>Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier</i> (Longitudinal Integrated Database for Health Insurance and Labour Market Studies)
MS	Multiple Sclerosis
NPR	National Patient Register
OR	Odds Ratio
RR	Rate Ratio
SLE	Systemic Lupus Erythematosus
TPR	Total Population Register



# 1 INTRODUCTION

In recent years, more and more people are aware of the importance of mental health, alongside physical health, to our overall well-being. The inclusion of mental health as one of the targets in the Sustainable Development Goals is an acknowledgement of this importance (1). This is warranted, given that mental illness, including substance use disorders, contributes to a substantial amount of the global disease burden. In 2019, around 1 billion people were affected by mental illness globally during the past year, an increase of more than 40% from the estimates in 1990 (2). The burden associated with mental illness is highest among younger adults (20-34 years), where 15% of the disease burden (measured as disability-adjusted life years) within this age group is due to mental illness (2). Incidentally, this is also the age group where many people would start a new phase in life, including becoming a parent (3).

Previous studies have shown that mental illness is common among parents (4–6). A review of international studies among adults using psychiatric services found that between 12-45% of these individuals were parents (6). Another cross-sectional study in Norway found that 36% of individuals in the specialised mental health outpatient clinics had children under the age of 18 (5). This study also found that the most common diagnoses among these individuals were anxiety disorders, behavioural and emotional disorders, and affective disorders (5). A survey from the US found that the one-year prevalence of any mental illness among parents was 18% (4). The same study also showed that 3.8% of the parents had serious mental illness and that the prevalence was higher among mothers (for both any and serious mental illness), compared to fathers (4).

When a parent has a mental illness, it is likely that the whole family, including the children, will be affected (7). Indeed, some studies have been conducted to investigate the potential consequences of parental mental illness to children. However, until recently, most of these studies focused more on the mental health outcomes of the children (8–18). These studies have generally shown that children with parental mental illness were at higher risk for developing behavioural problems (14–16,18) or mental illness themselves (8–13,17,18).

It is also likely that children and adolescents with parental mental illness (CAPRI) might experience adverse outcomes beyond the mental health domain, namely physical ill-health and worse social outcomes, but this is less clear. Unfortunately, it has been acknowledged that there is a lack of systematic attention on health and social outcomes in these children, even at the broader European level (19). While most CAPRI will remain resilient (19), identifying CAPRI who might be at risk for adverse health and social outcomes is essential to direct policy and practice to aid in targeting interventions for this vulnerable group.



## **2 LITERATURE REVIEW**

### **2.1 PREVALENCE OF CAPRI**

Given how common the mental illness is presented among parents, children of these parents might also be a population with considerable size, although the estimated prevalence might vary. A study in the UK using data from a primary care register found that approximately 23.2% of children aged 0-16 years had mothers with mental illness (20). In Australia, a 2009 study using 3 different data sources (2 surveys and 1 register) estimated that 23.3% of children lived in families with parental mental illness (21). However, a more recent Australian survey among children aged 4-17 years in 2013-2014 found that 37.2% of children had primary carers (the majority being biological mothers) with self-reported mental health problems (22). Another Canadian survey estimated that 12.1% of children under 12 years were exposed to parental substance use, mood, or anxiety disorders (23). Differences in the estimates might be attributed to different factors, including, for example, data sources, meaning that these estimates might not be directly generalised to another setting, for example in Sweden. There was also limited information about the prevalence among children with paternal mental illness and no reliable estimates about the prevalence in Sweden were available at the time this PhD project started. These motivated us to ascertain the prevalence of CAPRI specifically within contemporary Swedish settings.

### **2.2 PHYSICAL HEALTH OUTCOMES AMONG CAPRI**

To date, there has been only a limited number of studies examining the physical health of CAPRI. One very recent systematic review and meta-analysis found that CAPRI might have a higher risk for injuries and asthma (24). However, the majority of the studies included in this meta-analysis considered only maternal mental illness exposure, mainly maternal post-natal depression, and health outcomes among younger children (24). The study concluded that knowledge on the physical health of children with parental mental illness is very limited and more studies are needed. Two Danish studies investigated the association between parental serious mental illness (schizophrenia, bipolar disorder, unipolar depression) and the risk of somatic morbidity in the offspring using secondary care registers, one study focusing on the offspring up to 30 years of age (25), and the other one focusing on children 0-6 years (10). The first study found a 13% increased risk for any type of somatic morbidity in the offspring when they were exposed to parental schizophrenia, bipolar disorder, or unipolar depression (25). However, the risk appeared to vary by type of disease in the offspring; for example, no difference was detected in the risk for cancer between children with and without parental serious mental illness, but a large increase in risk for intentional self-harm among children compared to children without parental serious mental illness (25). The second study found that parental serious mental illness, except for paternal bipolar disorders, was associated with a 10-28% increased risk of any somatic disorders diagnoses in children up to

6 years of age (10). This study also found variations in risk by type of somatic disorders, with the highest risk being observed for diseases of the digestive system (10).

Based on previous literature and the identified knowledge gaps (see below under respective physical health outcomes) this PhD project focused on three physical health outcomes among CAPRI: injury, autoimmune diseases, and cancer.

### **2.2.1 Injury**

Injury is one of the leading causes of mortality and morbidity among children and adolescents worldwide. Injury is the number one cause of death among children and adolescents ages 1-19 years globally, accounting for 10-40% of deaths within this age group (2). In Sweden, around 25% of deaths among children aged 0-17 years are due to injury and this figure increases with age, with adolescents, aged 16-17 years, having the highest proportion of deaths due to injuries (60%) (26). Injury is also the most common cause of hospitalisation among children up to 17 years of age in Sweden, with approximately 16% of children in these ages having been hospitalised due to injury in 2016 (27). Further, boys are more likely to be hospitalised due to injury compared to girls (26). The number of deaths and hospitalisation due to injury has been decreasing over the last two decades in Sweden, and the decrease has been steeper for deaths (27).

Injury can be classified in many different ways, but it is often classified into unintentional injury (as a result of events not intended to cause injury, often called accidents) and intentional injury (as a result of events intended to injure another person or oneself) (28). Further, injury is often classified by the external cause(s) that lead to the injury, i.e. transport injury, fall-, burn-, and injury inflicted by violence (28,29). These classifications might be particularly useful within public health, given that different causes reflect different contextual risk factors, which might be targeted for injury prevention.

Also, as children age, the type of injury and the context in which injury occurs might change. For example, in the US, the most common cause of death due to injury, among children aged 1-4 years, is unintentional drowning; yet from age 5 until 24, the most common cause is traffic injury (30). Even within the same type of injury, the context to which the injury might occur differs by age group (28). For example, in the case of road traffic injury, children are more likely to be hospitalised as cyclists in the younger age groups, yet as they approach adolescence, they are more likely to be hospitalised as moped riders (28). Similarly, in the ages 0-3 years, most injuries (the most common type in these ages being fall injury), would occur at home, yet in the age group 13-17 years, most injuries would occur during physical activity, followed by traffic (28).

### *2.2.1.1 Mental illness and injury*

Most studies on the association between mental illness and the risk of injury have focused more on the context of self-harm (31) or suicide (32,33). Indeed, a large proportion (up to 80%) of people who died by suicide or who were admitted to the hospital due to self-harm had some form of mental illness (31,32). Research has consistently shown that mental illness is a risk factor for suicidal behaviour among adolescents and young adults (33).

Another area that is often studied within the context of mental illness and injury is the risk of interpersonal violence. Several studies have indicated that mental illness diagnoses are often associated with an increased risk of violence perpetration (34–38) and of being victims of violence (34,38,39). However, the absolute risk for violence perpetration among individuals with mental illness is usually low (35,36,38). Additionally, other studies showed that treatment with certain medications (e.g. antipsychotics and mood stabilisers), might be beneficial in reducing violent crime among people with mental illness (40,41).

There are fewer studies on the risk of unintentional injuries among adults with mental illness. One study in Taiwan reported that more patients with major depressive disorder reported unintentional injury in the past year compared to other patients in the same psychiatric outpatient clinic (42). Nevertheless, among children and adolescents, the risk of unintentional injury has been specifically studied in relation to attention deficit hyperactivity disorder (ADHD). One meta-analysis found that children and adolescents with ADHD had approximately 50% higher risk for unintentional injuries compared to children and adolescents without ADHD (43). Interestingly, the same study also showed that ADHD medications use was associated with a lower risk of unintentional injuries among these children (43).

### *2.2.1.2 Parental mental illness and injury*

Several studies investigated the risk of injuries among CAPRI (10,44–61) or children living with adults with mental illness (62). One study looked at any diagnosis of mental illness (53), while others focused only on serious mental illness (10,49), or individual diagnoses such as schizophrenia (48,52), substance misuse (47,50,55), and depression (44–46,51,54,56–61). In general, results from these studies suggested that parental mental illness were associated with an increased risk of injuries among the children. However, most of these studies investigated only mental illness among the mothers (44–46,48,50–54,56–60) and injury among younger children (10,45,46,48,49,53,55–59). There were also a limited number of studies investigating the risk in different types of injury (10,44,56,57,59). No single study has been carried out to investigate the risk for a wide range of parental mental illness among mothers and fathers beyond the diagnoses mentioned above, for different types of injuries, and throughout different child age groups.

## **2.2.2 Autoimmune disease**

Autoimmune diseases occur when the immune system mistakenly attacks the body's tissue (63). There are more than 80 different types of autoimmune diseases currently known (64). Some diseases, such as type 1 diabetes (65) and juvenile idiopathic arthritis (JIA) (66) are more commonly diagnosed among children and adolescents. For type 1 diabetes, the highest incidence is observed in the age group 10-14 years (65), while juvenile idiopathic arthritis is usually diagnosed before the age of 16 (66). For other diseases, such as systemic lupus erythematosus (SLE), the diagnosis is usually made during adulthood (67,68), yet childhood-onset SLE still contributes to a quite large proportion (approximately 10-20%) of all SLE cases (69).

Autoimmune diseases are generally considered rare diseases, but the prevalence and incidence might vary by age, sex, and world region. In the case of type 1 diabetes, it is estimated that there are 651,700 children and adolescents 0-14 years with type 1 diabetes in 2021 globally, and the majority of the cases are in Europe (70). In Sweden, 44 in 100,000 children aged 0-14 years are diagnosed with type 1 diabetes every year, making Sweden the country with the second-highest incidence of type 1 diabetes in children worldwide (70). Another study also found that the incidence of type 1 diabetes in Sweden peaks at different ages for boys (10-14 years) than girls (5-9 years) (71). For JIA, it is estimated that 8 in 100,000 children under 18 years receive a JIA diagnosis every year worldwide (72). In general, the estimated prevalence and incidence for JIA is higher among girls compared to boys (72). In Sweden, it is estimated that 14-15 in 100,000 children are diagnosed with JIA every year (73).

Autoimmune diseases in children and adolescents pose many challenges to the life of the affected individuals and their families. Apart from the high cost associated with diagnosis and treatment of the diseases (74), childhood-onset autoimmune diseases mean that children might experience a longer disease duration of the disease course compared with adult-onset autoimmune disorders (69). Some studies have also shown the lower quality of life among children and adolescents with autoimmune diseases and their families (69,74,75). Additionally, children with autoimmune diseases might face barriers to participating in school activities, which might contribute to the development of social anxiety and negative school and social outcomes among these children (76).

### *2.2.2.1 Mental illness and autoimmune disease*

Previous studies on mental illness and autoimmune diseases have primarily looked at the association of both diseases as a comorbid condition in index persons or looked at the mental illness as a consequence of autoimmune diseases (77,78). There have also been studies showing that mental illness was associated with subsequent risk of autoimmune diseases (77–88).

The majority of studies on the association between mental illness and subsequent risk of autoimmune diseases have looked at depression (79,81,85,87,88). In those studies, depression was associated with a higher risk of any autoimmune disease (85,88), psoriasis (85,87), SLE (81,85), and rheumatoid arthritis (79,85). Two studies found a 20-60% increased risk of autoimmune diseases among people with stress-related disorders (82,83). Two studies, one of which is a meta-analysis, found a 50% increase in the risk of autoimmune diseases among people with psychotic disorders (77,86). There were two studies assessing the risk of autoimmune diseases among people with eating disorders and it showed an overall increased risk, but the risk varied by type of autoimmune diseases (84). There was little evidence on the associations between ADHD and the risk of rheumatoid arthritis or inflammatory bowel disease (80).

#### *2.2.2.2 Parental mental illness and autoimmune disease*

Prior evidence on an association between parental mental illness and the risk of autoimmune diseases among offspring has been very limited (86,89). A Danish study found that having first-degree relatives (parents/siblings) with schizophrenia was associated with a 6% increased risk for any type of autoimmune disease (86). However, the risks differed by type of autoimmune diseases, with diseases such as SLE showing an up to 47% increased risk while the risk was lower for type 1 diabetes (around 12% increased risk), and there was also a slightly decreased risk (9%) for juvenile arthritis (86). On the other hand, a Swedish study found that offspring of parents with schizophrenia or schizoaffective disorder had a slightly lower risk for rheumatoid arthritis, but they had an increased risk for ankylosing spondylitis (89). The same study also found that there were no differences in the risk for rheumatoid arthritis among offspring of parents with bipolar disorder and only a slight increase in the risk for ankylosing spondylitis (89). No previous study before the study included in this thesis had specifically examined the risk of all types of autoimmune disorders in children and adolescents by type of maternal and paternal mental illness.

### **2.2.3 Cancer**

Cancer is an umbrella term for a group of diseases where some cells within the body start dividing uncontrollably and spread into other parts of the body (90). It is estimated that there are 140.6 new cases of cancer per million person-years among children aged 0-14 and 185.3 new cases per million person-years among adolescents aged 15-19 years worldwide (91). The most common cancer types in children 0-14 years are leukaemia, tumours of the central nervous system, and lymphomas, while for the older age group (15-19 years) most common cancer types are lymphomas and epithelial tumours and melanoma (91). The incidence rates of childhood cancer vary by sex and world region, with boys having slightly higher incidence rates compared to girls, and European regions having relatively higher overall incidence rates (91). In Sweden, the age-standardised (by European population) incidence rate for any type of

cancer among children and adolescents aged 0-19 years were 17.9/100,000 person-years for boys and 17.1/100,000 person-years for girls in 2020 (92).

Cancer does not usually occur in childhood, but when it does, it is usually more aggressive and requires specialised treatment (91,93). While the prognosis of many types of childhood cancers has improved in recent decades (93,94), additional challenges often present among children and their families following a cancer diagnosis. Childhood cancer might negatively impact the children's psychological well-being, ranging from increased irritability among toddlers to increased risk for risk-taking behaviours among adolescents (95). Some studies have indicated that the impact of childhood cancer might last well into adulthood, including a higher risk for chronic health conditions and mental illness (96,97). There have also been studies showing that the quality of life of the children and parents was negatively impacted by childhood cancer (98,99).

#### *2.2.3.1 Mental illness and cancer*

The majority of previous studies on the association between mental illness and cancer have focussed on mental illness as a consequence of cancer (100). A meta-analysis estimated that approximately 16% of cancer patients in hospital settings had depression and the respective prevalence for anxiety disorders was 10% (101). Nevertheless, there have also been studies that investigated the risk of cancer among people with mental illness (102–109).

Studies on mental illness and subsequent risk of cancer have generally shown mixed results. A Danish study (107) showed that certain mental illness diagnoses (schizophrenia, substance use disorders, mood disorders, stress-related disorders, eating disorders, and personality disorders) were associated with increased risk of cancer, while others, including ADHD, autism spectrum disorders, intellectual disabilities were not. A meta-analysis of cohort studies on the risk of cancer among patients with schizophrenia found an overall decreased risk, although the risk varied by types of cancer and sex (102). Another meta-analysis of cohort studies found a 30% increased risk of breast cancer among women with schizophrenia (103). Two Swedish studies found an increased incidence of breast and cervical cancer among women with substance use disorders (108,109). A meta-analysis of studies among individuals with depression found a 20% increased risk for cancer (104). A study combining data from Denmark, Finland, and Sweden found a slightly decreased overall risk of cancer among women with anorexia nervosa, but not among men (105). The same study also found a decreased risk for breast cancer among women with anorexia nervosa (105). On the other hand, a Danish study did not find an association between posttraumatic stress disorders and the risk of cancer (106).

Several hypotheses have been proposed to explain the association between mental illness and the risk of cancer. The risk might be influenced by factors commonly seen in both people with mental illness and cancer, such as smoking or diet (102–104,108,109). Barriers in accessing healthcare, including screening for cancer has also been proposed as a potential

contributing factor (108,109). Certain medications, such as antipsychotics, have also been suggested to influence endocrine hormones and thus affecting the risk of cancers among people with schizophrenia (102,103). Another hypothesis is that low energy intake and a high level of physical activity among people with eating disorders might influence particular hormones and lead to a decreased risk of certain hormone-related types of cancer among this population (105). On the other hand, stress has been suggested to also impair the immune system and thus affecting the body's ability to fight cancer (106). Finally, genetic components might play a role in the association between mental illness and cancer (104).

### *2.2.3.2 Parental mental illness and cancer*

There was limited knowledge on the potential associations between parental mental illness and the risk of cancer among the offspring. While two meta-analyses (110,111) and a cohort study (112) reported a potential increase in risk for cancer among the offspring associated with maternal or paternal alcohol or substance use, no studies investigated the associations for diagnosis of alcohol or substance misuse. A Danish study, which included 2 million individuals, reported little evidence of the association between parental serious mental illness (schizophrenia, bipolar disorder, or unipolar depression) and the risk of cancer among the offspring up to 30 years of age (25). However, this study (25) included also cancer diagnosed within the adult offspring, which might have different aetiology than the ones diagnosed among children and adolescents. Additionally, this study (25) combined different types of parental mental illness, and we hypothesised, based on other studies within the field of mental illness and cancer, that there might be differences in the associations based on types of mental illness. Studying the associations for different types of (mental illness) diagnoses separately might require an even larger sample size to achieve statistical power. Therefore, we strived to achieve this by combining the estimates from two large cohorts from Sweden and England.

## **2.3 SOCIAL OUTCOMES AMONG CAPRI**

When considering the consequences of parental mental illness to the life of their children, it is important to not only consider it in terms of their health (mental and physical health) but also regarding their social circumstances. CAPRI are more likely than other children to face multiple adversities (113–115) which might influence their risk for various unfavourable social outcomes. In this thesis, we focused on socioeconomic adversity and out-of-home care placement as potential social outcomes among children who have parents with mental illness.

### **2.3.1 Socioeconomic adversity**

Human beings exist in societies. To know where we are or where we belong in society, we are often grouped based on various social and economic factors, often known as

socioeconomic position (116). There are many indicators for determining someone's socioeconomic position, for example, education, employment, and income (116). Since these factors often change over time, it is important to consider what kind of indicators might be best suited to capture the socioeconomic position of a person at a certain point in time. For example, when studying socioeconomic position in childhood, we might use parental education or household income as indicators (116), since children are likely to be dependent on the situations and resources available from the parents and families.

These various social and economic indicators are often grouped into ordered categories, i.e., from low to high. When people are grouped into lower socioeconomic positions, they might be considered as having socioeconomic disadvantage or socioeconomic adversity. Additionally, studies have consistently shown that socioeconomic adversity is linked to poorer health, including mental health (117).

#### *2.3.1.1 Mental illness and socioeconomic adversity*

There are two main hypotheses on how mental illness and socioeconomic adversity might be linked (117). The first one, referred to as 'social causation', states that socioeconomic adversity and its consequences such as stress and financial insecurity might lead to the development of mental illness (117). For example, many studies have shown that lower socioeconomic position is associated with an increased risk of incident depression (118,119). The second hypothesis, referred to as 'social drift', states that mental illness might lead individuals into lower socioeconomic positions (117). For example, some studies have shown that mental illness in adolescence is associated with a higher risk of school dropout and unemployment in adult age (120,121). Naturally, all these associations are likely to be complex and might influence one another throughout the life course. There might also be differences in the strengths of associations based on the type of socioeconomic indicators and mental illness.

#### *2.3.1.2 Parental mental illness and socioeconomic adversity*

Given what we know about the association between mental illness and socioeconomic adversity, when parents experience mental illness, they may also experience socioeconomic adversity. Since children are largely dependent on their parents, such adversity might also impact the children. Understanding how these conditions, i.e., parental mental illness and experience of socioeconomic adversity, co-occur among children is important, given that socioeconomic adversity is likely to act as an effect modifier on any possible consequence of parental mental illness on children's health and life outcomes (15). However, studies specifically assessing children's concurrent experience of both parental mental illness and socioeconomic adversity are rare. One previous study from the US reported that parents with mental illness were more likely to be unemployed, received government welfare assistance,



and live in poverty compared to parents without mental illness (114). Another Danish study reported that children of parents with serious mental illness were less likely to live with both parents when they grew up (122). Among adult offspring, a Swedish study found that exposure to parental substance use disorders during childhood was associated with being not in education, employment, or training during young adulthood (123).

### **2.3.2 Out-of-home care placement**

Out-of-home care refers to the temporary or permanent placement of the children apart from their parents due to adverse family conditions or children's behaviour (124). In Sweden, child welfare measures, including the decision to place a child in care outside of their home falls into the responsibility of the Social Welfare Board within each municipality (125,126). There are two legal bases for placement in out-of-home care, either voluntarily through the Social Services Act (127) or by court order through the Care of Young Persons (Special Provisions) Act (128).

In 2020, around 17,000 children and adolescents aged 0-17 were placed in out-of-home care in Sweden (approximately 1% of the total children population), the majority being boys above 15 years of age (129,130). Most of these children were placed in a foster home, followed by a care home, support housing, other forms of placement, and special supervisory homes (129). About 70% of these children were placed voluntarily based on the Social Services Act (129).

While out-of-home care placement is judged as necessary to ensure a child's welfare, this measure might impact both the children and the family in both the short and long term. Children in out-of-home care might have poorer overall physical and mental health outcomes (131) and this might last well into adulthood (124,132–135). Adult offspring with a history of out-of-home care placement might also have poorer social outcomes (135,136). Other studies have shown that having children taken into out-of-home care can traumatise mothers (137), and is associated with poorer health and social outcomes for the parents (138–141).

#### *2.3.2.1 Parental mental illness and out-of-home care placement*

Several studies investigated the association between parental mental illness and the likelihood of the children to be taken into care outside their home (141–149). Overall, these studies indicated that there is an increased likelihood for the children whose parents have mental illness to be placed in out-of-home care, sometimes even at birth or discharge (141,146,147). However, the majority of the studies looked only at maternal mental illness (141,143,146–149), with maternal schizophrenia being the most commonly studied diagnosis (141,142,144,146–149), followed by maternal depression (141,142,144,146,148). There is a need to understand better how paternal exposure and other types of mental illness might play

a role in the likelihood of out-of-home care placement among the offspring. In studies assessing multiple diagnoses of mental illness, it has been indicated that more serious mental illness such as schizophrenia was often associated with a relatively higher risk for placement in out-of-home care compared to other diagnoses (141,142,146). There is a paucity of studies examining certain diagnoses, for example, neurodevelopmental disorders, although it has been indicated previously that a substantial proportion of children of parents with these diagnoses (e.g., maternal intellectual disability) were not primarily raised by their biological parents (150). Moreover, there is a need to obtain a better picture within the contemporary Swedish context, given the fact that the last study within this area was conducted more than a decade ago (145).

### 2.3.2.2 *Factors related to out-of-home care placement*

While parental mental illness might be considered as one of the contributing factors for out-of-home care placement for the children, there might be other factors that could play a role in making such decisions. Several studies have tried to identify such risk factors (141–146), which will be summarised below. In general, these factors might be classified into demographics, socioeconomic, and other health or social factors.

#### 2.3.2.2.1 Demographics

Several demographic factors have been studied in relation to children's placement in out-of-home care. One study found that increasing child age was associated with a higher risk of placement (142), while another study showed the opposite direction (144). There also seems to be mixed results with regards to the child's sex, with one study showing a slightly increased risk for boys (144) and another showing a slightly increased risk for girls (145), although these differences might be due to differences in the social context and services between countries. Additionally, ethnicity might also play a role, at least in the US context, since African American children have been shown to have a higher risk for placement in out-of-home care compared to white children (144).

The majority of studies on parental demographics as predictors for a child's placement in out-of-home care have focused on the mothers' characteristics. A Swedish study showed that children who were born to non-Swedish-born mothers had a lower risk for placement in out-of-home care (145). On the other hand, the associations with maternal age have been inconclusive; some studies have found a higher risk for teenage mothers (141,145), one study showed slightly decreased risk with increasing maternal age (146), another showed increased risk with increasing age (144), and another showed no association (143). Being born in an urban neighbourhood were more consistently associated with an increased risk of out-of-home care placement in children in studies from Sweden and Canada (141,145). Additionally, having mothers living in non-owned residences (renting/institution/homeless)

(143) or having mothers in unstable housing situations (141) were also associated with increased risk for placement in out-of-home care in Finland and Canada. The majority of studies from developed countries also showed that having single-parent mothers was associated with a higher risk of placement in out-of-home care (142,145,146), although one study from Finland showed no association (143).

#### 2.3.2.2.2 Socioeconomic position

Similar to studies on demographic risk factors, most studies assessing parental socioeconomic position as potential predictors of out-of-home care placement among the offspring only take into account maternal socioeconomic position. Low maternal education and unemployment status were consistently shown as risk factors for the children's placement in out-of-home care (142–145), and it was likely applied to the fathers as well (142). Maternal low income and receipt of disability pension were also considered risk factors for out-of-home care placement among the children (142,144–146). On the other hand, the evidence regarding maternal receipt of sickness benefits or social welfare benefits is mixed (141,142,145,146). There has also been one study showing that a lower neighbourhood socioeconomic index was associated with a higher risk for out-of-home care placement (141).

#### 2.3.2.2.3 Other health and social factors

Some physical health-related factors might also influence a child's risk of placement in out-of-home care. Neonatal complications (146), neonatal abstinence syndrome symptoms and treatment, admittance to neonatal intensive care unit, delayed hospital discharge after delivery (143) and receiving inadequate or no prenatal care (141) were all associated with increased risk of placement in out-of-home care in previous studies. The same could also be said for reports of physical abuse and neglect in children (144). On the other hand, increased gestational age was associated with a lower risk of out-of-home care placement in one previous study (141).

Apart from parental mental health status, parental physical health status has also been studied in the context of children's risk for out-of-home care placement. Maternal hepatitis B or C and some perinatal factors such as parity, smoking, and alcohol- and drug use during pregnancy or before were among the factors that were linked with increased risk for out-of-home care placement for the offspring (143).

Apart from parental physical health, other studied factors that might influence the risk for out-of-home care placement include maternal involvement in the criminal justice system (141), maternal relationship with a partner, own mother, or close confidant (146), and parental history of out-of-home care placement (143,151).

Taken together, previous studies have shown complex associations between several factors, apart from parental mental illness, with children's risk of placement of children in out-of-home care. Even among families with parental mental illness, there might be differences in the likelihood for the children to be placed in out-of-home care based on the co-existence of other risk factors. Since there has been limited information on this issue within the contemporary Swedish context, one of the studies within this project (Study V) was dedicated to clarifying which factors might modify the likelihood for out-of-home care placement among children with parental mental illness.



### **3 RESEARCH AIMS**

The overall aim of this doctoral project was to estimate the prevalence of children and adolescents with parental mental illness (CAPRI) and to increase the relevant knowledge base about the consequences of parental mental illness for CAPRI's health and social outcomes.

More specifically, our individual studies sought to address the following questions:

1. What is the proportion of children and adolescents whose mothers or fathers received mental illness diagnoses within secondary care in Sweden, overall, and by type of mental illness diagnosis? Does the proportion vary over time? Do these young people have a higher risk of socioeconomic adversity?
2. What are the risks of injury associated with parental mental illness? Are there differences in risks by age, parental diagnosis, maternal or paternal exposures, and types of injury?
3. What are the risks of childhood autoimmune disease associated with parental mental illness? Are there differences in the risks by type of parental diagnosis, maternal or paternal exposures, and types of autoimmune disease?
4. What are the risks of childhood cancer associated with parental mental illness? Are there differences in the risks by type of parental diagnosis and maternal or paternal exposures?
5. What are the risks of out-of-home care placement associated with parental mental illness? Are there differences in the risks by age of the child, type of parental diagnosis, maternal or paternal exposures? What are the factors that might modify the risk of out-of-home care placement among these young people?

## **4 MATERIALS AND METHODS**

We conducted five cohort studies in this thesis. In addition, in Study I, we included cross-sectional analysis of the study population, and in Study IV we also performed a pooled data analysis with English data. An overview of the methods used in the studies can be seen in Table 4.1 and Figure 4.1.

Table 4.1 Summary table with methods elements for Studies I-V

Theme	Study	Study population	Start of follow up	End of follow up	Main exposure period	Main outcome	Analytical approach
Prevalence and social outcomes	I, Prevalence and socioeconomic adversity	Children born in Sweden 1991-2011 (n=2,110,988), their mothers (n=1,179,754), and fathers (n=1,171,497)	Birth or 1 January 2006 (whichever was latest)	Death (children or both parents), emigration (children or both parents), age 18, or 31 December 2016 (whichever was earliest)	Parental mental illness during follow up	- Prevalence of children with parental mental illness - Risk of socioeconomic adversity	Logistic regression
Physical health outcomes	V, Out-of-home care placement	Children born in Sweden 2000-2011 (n=1,249,463), their mothers (n=778,170), and fathers (n=765,843)	Birth	First out-of-home care placement, death (children or either parent), emigration (children or either parent), or 31 December 2016 (whichever was earliest)	Parental mental illness from 3 years before birth until the end of follow up	- First out-of-home care placement - Effect modifiers for out-of-home care placement	Cox proportional hazard regression
Physical health outcomes	II, Injuries	Children living in Sweden born 1996-2011 (n=1,542,000), their mothers (n=893,334), and fathers (n=873,935)	Birth or 5 years after parents' immigration (whichever was latest)	Death (children or either parent), emigration (either parent), age 18, or 31 December 2016 (whichever was earliest)	Parental mental illness from 5 years before the start of follow up until the end of follow up	Rate of injuries	Poisson regression
Physical health outcomes	III, Autoimmune diseases	Children born in Sweden 1991-2011 (n=2,192,490), their mothers (n=1,224,238), and fathers (n=1,207,810)	Birth	First diagnosis of autoimmune disease, death (children or either parent), emigration (children or either parent), age 18, or 31 December 2016 (whichever was earliest)	Parental mental illness from 1 year before birth until the end of follow up	First diagnosis of autoimmune disease	Cox proportional hazard regression



IV, Cancer	Birth	First diagnosis of cancer, death (children or either parent), emigration (children or either parent), age 18, or 31 December 2016 (whichever was earliest)	Parental mental illness from 1 year before birth until the end of follow up	First diagnosis of cancer	- Cox proportional hazard regression
- Children born in Sweden 1991-2011 (n=2,192,476), their mothers (n=1,224,239), and fathers (n=1,207,810) - Children living in England born 1996-2017 (n=591,092) and their mothers (n=418,944)	Birth, registration at general practice, the start of data collection at general practice, or 1 April 1997 (whichever was latest)	First diagnosis of cancer, transferred out of general practice, end of data collection at general practice, death (children or mother), age 18, or 31 July 2017 (whichever was earliest)			- Bayesian meta-analysis

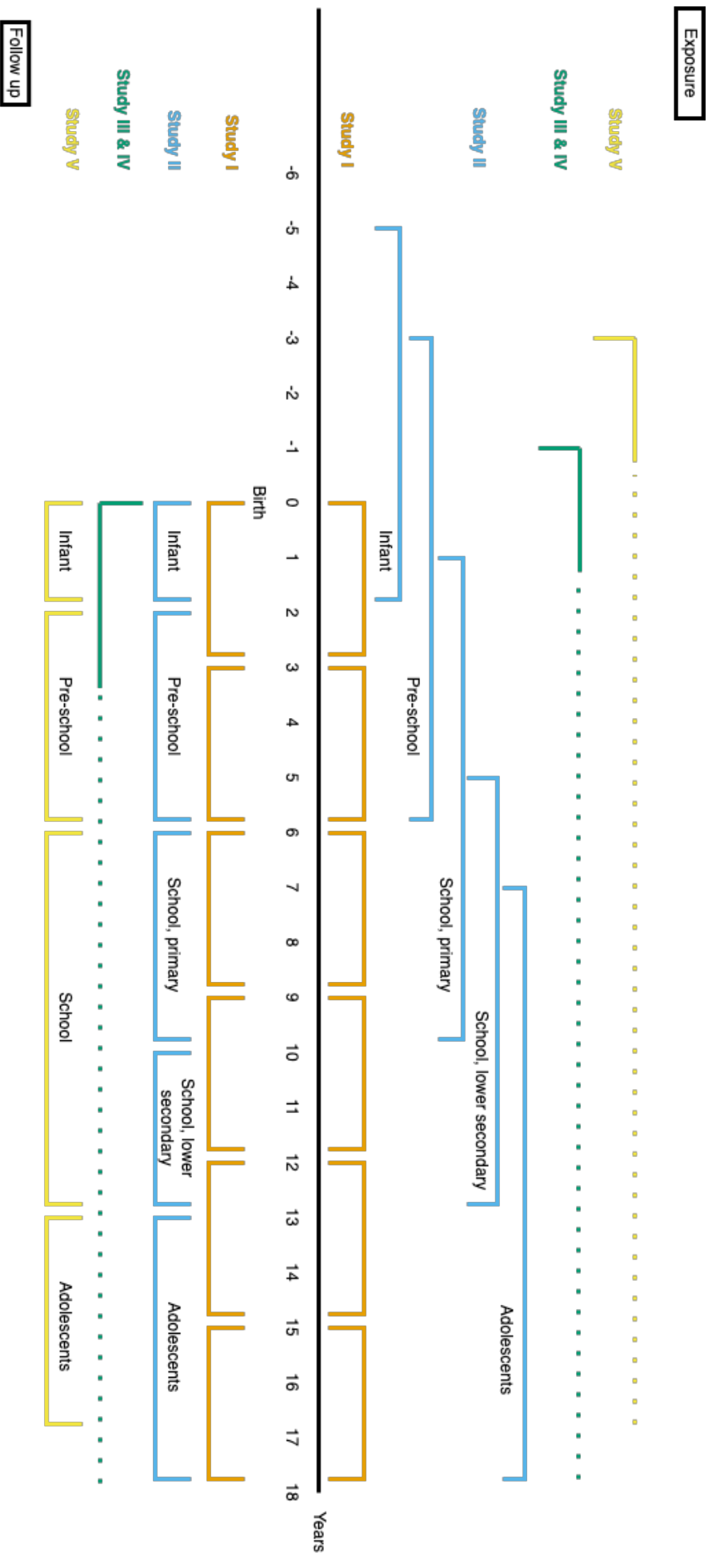


Figure 4.1 Overview on the timeline for main exposure measurements and follow up for Studies I-V

## 4.1 DATA SOURCES

All five studies in this thesis were based on a linkage of various Swedish national registers called 'Psychiatry Sweden' that is described below. The linkage was made possible using the unique personal identification number (*personnummer*) assigned to all Swedish residents (152). Registers included in 'Psychiatry Sweden' that were used for this thesis were:

- The Total Population Register (*Registret över totalbefolkningen*, TPR, available from 1968. This register contains demographic information of virtually all Swedish residents, including date of birth, country of birth, sex, date of migration to/from Sweden, and date of death (153).
- The Multi-Generation Register (*Flergenerationsregistret*). This register contains information on the parental relationships (biological and adoptive) for all individuals born from 1932 who have been registered in Sweden at some point since 1961 (154,155).
- The National Patient Register (*Patientregistret*, NPR). This register contains information on inpatient and specialised outpatient visits (non-primary care) within the Swedish healthcare system (156,157). Information available include date of admission and discharge (inpatient), date of visit (outpatient), as well as main and secondary diagnoses in the Swedish version of ICD-codes (156,157). Since 1987, this register has had complete coverage for inpatient care (156,157). However, information on specialised outpatient visits was not available until 2001 (156,157).
- The Swedish Cancer Register (*Cancerregistret*). Available from 1958, this register contains information on malignant and certain benign tumours in the whole Swedish population (158,159). The information available includes the date of diagnosis and tumour site coded using the Swedish version of ICD-codes (158,159).
- The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (*Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier*, LISA), available from 1990. This register contains information on demographic and socioeconomic variables for all individuals aged 16 years and above in Sweden (15 years and above since 2010) (160,161). Information available include education, marital status, employment status, and income (including disposable income and social welfare benefits) and is updated annually (160,161).
- The National Child Welfare Register (*Registret över insatser till barn och unga*), available since 1982. This register contains information on out-of-home care placements reported by all Swedish municipalities among children and adolescents up to 20 years of age (162). Up until 2013, the registers included information for all children (162). However, in 2014–2016, only children with complete personal identification numbers were included, i.e., asylum-seekers were not included during this period (162). The information available includes the date and type of placement (voluntary or mandatory) (162).

- The Medical Birth Register (*Medicinska födelseregistret*), established in 1973. This register contains information from prenatal, delivery, and neonatal care throughout Sweden (163,164).

For Study IV, we also used a register linkage from the UK, namely the Clinical Research Practice Datalink (CPRD-GOLD), which contains information on visits to participating primary care (165). This was linked to the Hospital Episode Statistics (HES), which contains information on visits to the secondary care in the UK (165,166) and the Index of Multiple Deprivation 2010 (IMD 2010) database (167), which contains area-level information on deprivation. Record linkage was performed using specific identifiers and algorithms (168). This register linkage covers approximately 58% of all primary care in England (165). Individual-level data from the UK was available to be analysed by our UK collaborators and estimates obtained from these data were included to be pooled with the Swedish estimates, analysed by us.

## 4.2 STUDY POPULATION

All studies in this thesis include children born in Sweden between 1991-2011 identified using the TPR (for Study II we also included children born outside Sweden who, however, resided in Sweden). These children were then linked to their biological parents using the Multi-Generation Register and followed up until the latest 31 December 2016 (Table 4.1). We further divided the follow-up time by 3-year periods (Study I) or by child developmental period, namely infancy, pre-school, school age, and adolescence (Studies II and V, Figure 4.1).

In Study IV, we also identified children born on 1 January 1996-31 June 2017 and their mothers from the CPRD using the Mother-Baby Link algorithm (169).

## 4.3 MAIN MEASURES

### 4.3.1 Parental mental illness (Studies I-V)

In all studies, parental mental illness was defined using the following ICD-codes (Table 4.2), recorded as either primary or secondary diagnosis in the NPR.

Table 4.2 Parental mental illness diagnosis and corresponding ICD codes

Mental illness diagnosis	ICD-8 codes	ICD-9 codes	ICD-10 codes	Study
Psychotic disorders	295; 297;	295; 297;	F20-24; F28-	I-V
Non-affective psychotic disorders, including schizophrenia	298; excluding 295,70; 298,10	298; excluding 295H and 298B	29	
Affective psychotic disorders, including bipolar disorder	296; 295,70; 298,10	296; 295H; 298B	F25; F30-31; F32.3; F33.3	I-V
Alcohol/drug misuse	291; 294,30;	291; 292;	F10-16; F18-	I-V

		303; 304; excluding 303,00; 291,9	303; 304; excluding 291E; 292X	19; excluding 4th digit .0 and .9	
Common mental disorders	Depressive disorders, excluding those with psychotic symptoms	300,40	300E; 311	F32-34; F38-39; excluding F32.3 and F33.3	I-V
	Anxiety/stress-related disorders	300; 305; 306,0; 306,9; 307; excluding 300,40; 305,50	300A-D; 300F-H; 300W-X; 306; 307A; 308; 309	F40-48	I-V
Other mental illness	Eating disorders	30650; 30550	307B; 307F	F50	I-V
	Personality disorders	301	301	F60-63; F68-69	I-V
Neurodevelopmental disorders	Attention deficit hyperactivity disorder	308	314	F90	I, III-V
	Autism spectrum disorder	299	299	F84	III-V
	Intellectual disability	311-315	317-319	F70-79	V

For Study IV, we also identified maternal mental illness from the CPRD database using the procedure previously published (20). In short, maternal mental illness was identified through the presence of diagnosis, referral to psychiatric care, or from combinations of symptoms and psychotropic medications (20). Detailed code can be accessed in an online repository (170).

For all studies, we wanted to capture the most recent diagnosis of parental mental illness, hence the start of exposure ascertainment was at the latest 5 years before the start of follow up (Study II, see Table 4.1). Studies have shown high validity for mental illness diagnoses in the National Patient Register (156,171–175). For example, the positive predictive value for schizophrenia diagnosis ranged from 77-95% (156). For Study I, parental mental illness was identified overall during follow up, as well as within age and calendar period. For Study II, parental mental illness was identified from 5 years before a specific age period until the end of that specific period. We also identified parental mental illness diagnosed only during the 5-year period before each specific age period as a sensitivity analysis to rule out potential reverse causality. For Studies III-V, we identified parental mental illness as a time-varying exposure in which we identified diagnosis occurring from 1 (Studies III-IV) or 3 (Study V) years before birth and the children were considered exposed from the first date of such diagnosis. By doing this, we were hoping to take into account the nature of mental illness exposure, which might vary over time (i.e., episodic). However, for simplicity and given that mental illness largely recur or tend to be chronic, we considered those who were exposed to remain exposed until the end of follow up.

While the choice of a time-dependent exposure in these three studies enabled us to minimise the potential for reverse causality, (i.e., children were censored once the outcome occurred and so those exposed afterwards would not be considered in the exposed cohort), we also

conducted an additional sensitivity analysis by only including exposures that occurred before birth (Study III). This was done since we acknowledged that the date of diagnosis in the register might not be the same as the date of onset and there might be a delay in obtaining the diagnosis. Therefore, we also included exposures that were known to occur prior to birth (i.e., during a period where the outcome could not possibly occur). In Study IV, we included parental mental illness diagnosed before childbirth as a covariate for the Swedish estimates to account for the potential co-occurrence of mental illnesses.

#### 4.3.2 Injury (Study II)

We calculated the number of visits in the NPR with any of the following ICD-based injury codes during the follow-up period (Table 4.3). We used the codes for external causes of injury since it might be more useful from the public health or injury prevention perspectives to identify the causes of injury, rather than only identifying the injured body parts. We decided to focus on most injury types except for self-inflicted injuries such as self-harm and suicide since these types of injuries have been studied extensively elsewhere (176–178).

Table 4.3 Child injury and corresponding ICD codes

Type of injury		ICD-9	ICD-10
Unintentional	Transport injuries	E800-849	V01-V99
	Falls	E880-888	W00-W19
	Burns	E890-899, E919, E924	X00-X19
	Drowning and suffocation	E910-913	W65-W84
	Poisoning	E850-869	X40-X49
Intentional	Violence	E960-969	X85-Y09

#### 4.3.3 Autoimmune disease (Study III)

We identified the first diagnosis of autoimmune disease among children in the study population from the NPR using the ICD codes outlined below (Table 4.4).

Table 4.4 Children's autoimmune diseases and corresponding ICD codes

Autoimmune disease diagnosis	ICD-9	ICD-10
Type 1 diabetes mellitus	250	E10
Juvenile idiopathic arthritis (JIA)	714D	M08-09
Systemic lupus erythematosus (SLE)	710A	M32; excluding M32.0
Psoriasis	696A-B	L40
Multiple sclerosis (MS)	340	G35
Inflammatory bowel disease	555-556	K50-51
Coeliac disease	579A	K90.0

We also identified parental history of autoimmune disease as one of the covariates. It was defined as the presence of any autoimmune disease diagnosis (Table 4.5) in the mothers or fathers at any time point up until childbirth.

Table 4.5 Parental autoimmune diseases and corresponding ICD codes

Autoimmune disease diagnosis	ICD-8	ICD-9	ICD-10
Alopecia areata	704,00	704A	L63
Antiphospholipid syndrome			D68.6
Autoimmune haemolytic disease	283,90	283A	D59.1
Autoimmune thyroiditis	245,03	245C	E06.3
Behçet's disease	136,07	136B	M35.2
Coeliac disease	269,10	579A	K90.0
Giant cell arteritis	446,30; 446,38	446F	M31.5; M31.6
Guillain-Barré syndrome	357	357A	G61.0
Idiopathic thrombocytopenic purpura	287,10	287D	D69.3
Inflammatory bowel disease	563	555; 556	K50; K51
Multiple sclerosis (MS)	340	340	G35
Myasthenia gravis	733,00	358A	G70.0
Pemphigus and pemphigoid	694	694E; 694F	L10; L12
Pernicious anaemia	281,0	281A	D51.0
Primary adrenocortical insufficiency (Addison's disease)	255,10	255E	E27.1
Primary biliary cirrhosis		571G	K74.3
Psoriasis	696	696	L40
Inflammatory polyarthropathies and ankylosing spondylitis	712	714; 720	M05-M09; M45
Sarcoidosis			D86
Systemic lupus erythematosus (SLE), systemic sclerosis, Sjögren's syndrome, dermatomyositis, and other connective tissue disease	716; 734,0; 734,1; 734,9	710	M32.1; M32.8; M32.9; M33; M34; M35.0; M35.1
Thyrotoxicosis with diffuse goitre (Graves' disease)	242,00	242A	E05.0
Type 1 diabetes mellitus			E10
Granulomatosis with polyangiitis (Wegener's granulomatosis)	446,20	446E	M31.3

Previous studies have shown that the validity of autoimmune diseases diagnosis in the NPR is high, particularly when using  $\geq 2$  diagnoses as case definition (179–182). Therefore, we also conducted a sensitivity analysis by including only outcomes with at least 2 recorded diagnoses to minimise potential misclassification.

#### 4.3.4 Cancer (Study IV)

In the Swedish data, we identified the first diagnosis of childhood cancer during follow-up using ICD-9 codes (140-208) from the Swedish Cancer Register, which has shown to have high completeness (158). In English data, childhood cancer was identified using ICD-10 codes (C00-C97) from inpatient admissions from the Hospital Episode Statistics dataset. In Swedish data, we also identified parental history of cancer as one of the covariates. It was

defined as the presence of any cancer diagnosis using the ICD-9 codes (140-208) in the mothers or fathers at any time point up until childbirth.

#### 4.3.5 Socioeconomic adversity (Study I)

To quantify the association between parental mental illness and socioeconomic adversity, an age group for each child was randomly selected and the middle calendar year was identified for that age group. Indicators of socioeconomic adversity (Table 4.6) for this calendar year were extracted, except for teenage parenthood (which was measured at birth). For example, for a child who was born in 2010 and selected for age group 0-2 years, we would assign an indicator of socioeconomic adversity in the year 2011 for that particular child.

Table 4.6 Indicators for socioeconomic adversity

Indicator	Data source	Definition	Categories
Teenage parenthood	TPR	Mothers or fathers aged <18 years at the time of childbirth	Yes/no
Not living with parents	TPR	Children have the same family identifiers as mothers or fathers	Living with mothers: yes/no Living with fathers: yes/no
Neither parent educated at tertiary level	LISA	The highest attained education of mothers or fathers were first categorised into compulsory ( $\leq 9$ years), secondary (10-12 years), tertiary ( $\geq 13$ years) and then dichotomised.	Yes (tertiary education)/no (compulsory or secondary)
Parental unemployment	LISA	Both mothers and fathers were not employed.	Yes/no
Household receipt of social welfare benefits	LISA	Mothers or fathers received family social welfare benefits (161), which is the financial support given by the municipality for individuals unable to support their basic needs.	Yes/no
Household in lowest disposable income quintiles	LISA	Household disposable income is defined as the sum of all income of family members after taxes. Quintiles for household disposable income were calculated using the sample distribution for each calendar year and then further dichotomised.	Yes (Q1)/no (Q2-Q5)

While these indicators of socioeconomic adversity served as outcomes for Study I, we used some of the variables outlined above as covariates for Studies II-V. However, instead of the middle year of a certain age group, we measured these variables at the time of childbirth (Studies III-V) or 6 years prior to each child developmental period (Study II). The categorisation also differed slightly from the ones mentioned above. For example, we did not further dichotomise parental education and household income when these indicators were used as covariates.



#### **4.3.6 Out-of-home care placement (Study V)**

The first episode of out-of-home care placement among children in the study population during follow-up was identified using National Child Welfare Register. We also identified parental history of out-of-home care placement as a covariate, defined as the mothers or fathers having a record of out-of-home care placement at any time point up until childbirth.

#### **4.3.7 Other covariates**

We obtained information on children's sex (female/male), country of birth for children and the parents (Sweden/others), birth year (identified from the TPR), and the number of siblings (identified from Multi-Generation Register and TPR). We also identified the presence of childhood psychopathology throughout follow-up in the NPR using ICD-9 (291-309, 311-314, 316) or ICD-10 (F10-F69, F84, F90-95) codes. Parental marital status was obtained from LISA and defined as either parent being married or in registered partnership at the time of childbirth.

### **4.4 STATISTICAL ANALYSIS**

#### **4.4.1 Logistic regression**

Logistic regression is commonly used to model binary outcomes. In Study I, logistic regression was used together with marginal standardisation (183) to estimate the prevalence of parental mental illness (predicted probabilities) overall, by age period (Figure 4.1), and by calendar period (2006-2009, 2007-2010, 2008-2011, 2009-2012, 2010-2013, 2011-2014, 2012-2015, 2013-2016). Apart from predicted probabilities, logistic regression was used to model the association (quantified as odds ratio (OR)) between parental mental illness and indicators of socioeconomic adversity. Analysis for this study was performed using Stata (version MP 15.1) and R (version 3.4.1).

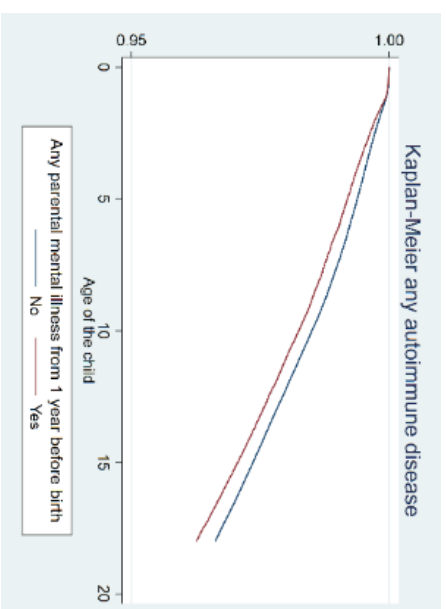
#### **4.4.2 Poisson regression**

Poisson regression is commonly used to model count data. In Study II, we used Poisson regression to model the association between exposure to parental mental illness and count number of injury visits during follow up time (rate of injury) using the age of the child as the time scale. We obtained the estimate in both additive (as rate difference) (184) and multiplicative scales (as rate ratio), to get the whole picture of associations (as absolute and relative measures). The estimates were stratified by age group (Figure 4.1) since there might

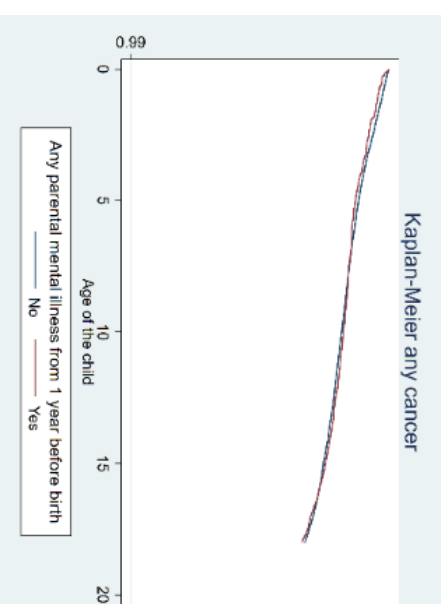
be differences in the injury pattern by age (28). Analysis for this study was performed using SAS (version 9.4) and R (version 3.6.1).

#### **4.4.3 Cox proportional hazards regression**

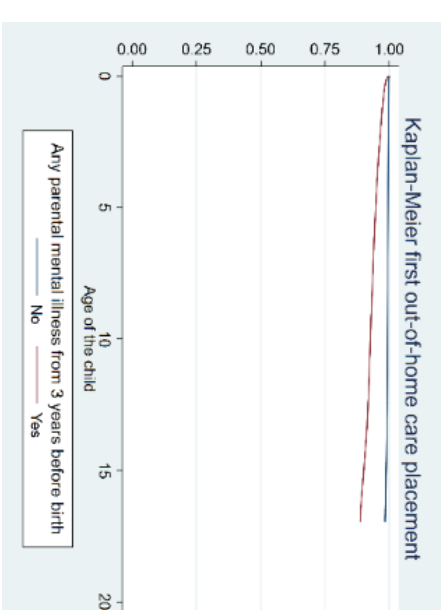
Cox proportional hazards regression (Cox regression) is commonly used to model time-to-event data. In Studies III-V, we used Cox regression to model the association between parental mental illness and time to the first diagnosis of autoimmune disease (Study III), cancer (Study IV), and out-of-home care placement (Study V), quantified as hazards ratio (HR). As the name indicates, it assumes that the ratio of the hazard (i.e., the speed in which the events occur) between unexposed and exposed would be proportional over time. One way to assess this assumption is by plotting the survivor function (Kaplan-Meier curves). If the assumption is not violated, we would see that the survivor curves are parallel over time. As shown in Figure 4.2, for Study III, the lines are relatively parallel over time, and so we assumed that violation of proportional hazard assumption is not a major concern here, especially since the pattern for survivor function is very close between exposed and unexposed (note that the y-axis scale has been truncated to give a better overview). For Study IV, we could see again that the survivor function is very close between exposed and unexposed, although at some point it started to cross. However, since this is very close to null (also note the y-axis scale), we assumed that this might be due to random variation and decided that there was not a substantial violation. In Study V, it could be seen that the gap between the exposed and unexposed becomes wider and wider over time, suggesting a potential violation of proportional hazards assumptions. Therefore, for this particular study, we decided to stratify the estimates by the follow-up time (outlined in Figure 4.1) by fitting in interaction terms with time in the model. Analyses for these studies were performed using SAS (version 9.4), Stata (version 16.1), and R (version 3.6.1, 4.1.2).



(A)



(B)



(C)

Figure 4.2 Kaplan-Meier curves for: (A) any autoimmune disease among those exposed and unexposed to any parental mental illness (Study III), (B) cancer among those exposed and unexposed to any parental mental illness (Sweden, Study IV), (C) out-of-home care placement among those exposed and unexposed to any parental mental illness (Study V). Note the difference in the y-axis scale.

#### 4.4.4 Bayesian random-effects meta-analysis

Meta-analysis is a method to obtain a single summary estimate when estimates from two or more studies, addressing a similar research question, are available. In Study IV, we were not able to combine individual-level data from Sweden and England, due to the ethical requirements of the datasets, yet we could obtain separate estimates for the association between maternal mental illness and cancer from both cohorts. A Bayesian random-effects model (185) was chosen since this method is suited when there are only a few studies available (186,187). Using this method might give us more robust, albeit more conservative (wider) interval estimates than the usual (frequentist) meta-analysis (186,187). Within the Bayesian framework, we need to specify *a priori* parameters (priors) for the summary effect size and the between-study standard deviation (heterogeneity) (185). Since there were few studies in the field of parental mental illness and childhood cancer, we decided to use uninformative prior for the summary effect size. On the other hand, the previous meta-analysis on the association between mental illness (schizophrenia) and risk of cancer showed relatively low heterogeneity ( $\tau^2=0.03$ ) (102). Therefore, we used a more conservative informative prior for the heterogeneity parameter set into  $\tau^2=0.04$  ( $\tau=0.2$ ) with half-normal distribution, reflecting low-to-moderate heterogeneity (188). We obtained pooled HR with 95% Credible Interval (CrI), which is the range in which there is a 95% probability that the true parameter would lie within. As a sensitivity analysis, we also conducted a sensitivity analysis by including different heterogeneity prior, ranging from very low ( $\tau=0.01$ ) to fairly extreme ( $\tau=1.00$ ) (188).

#### 4.5 ETHICAL CONSIDERATIONS

This doctoral project was intended to improve our knowledge about the extent of CAPRI prevalence, as well as understanding potential physical health and social outcomes among these offspring/young people. We utilised various Swedish national registers, including the TPR, Multi-Generation Register, NPR, Cancer Register, among others, to conduct the studies. In general, the processing of personal information, such as those included in these registers, are prohibited under the current General Data Protection Regulation, with certain exceptions. Processing of personal information, including sensitive personal information (e.g., health status) might be allowed for specific research purposes given that it has received ethical approval from the Ethical Review Authority. The studies in this project are included under the scope of ethical permission obtained for Psychiatry Sweden, a register linkage especially designed to study the occurrence, causes, and consequences of mental illness (DNR: 2010/1185-31/5, 2013/1118-32, 2016/987-32). Similar permissions were also obtained by the UK collaborators to utilise the relevant registers that are available there (Protocol Number: 17\_187).

There are four principles of ethics in biomedical research: ‘doing good’, ‘do no harm’, ‘respect for autonomy’, and ‘justice’. In terms of ‘doing good’, we did not give direct benefits

or compensation of any kind to the participants, since the studies were based on data that have already been collected. Hence, we were not directly doing good for the participants. However, by conducting the studies, we obtained new knowledge within the field, which in turn might be used to inform the policymakers or to design the prevention or intervention program to improve the health and social circumstances of the participants and society in general. With regards to ‘do no harm’, the participants avoided direct physical harm, since there were no invasive medical procedures or direct contact with them. However, the studies involved the processing of sensitive personal information (e.g., health information), which, if not handled carefully, might violate the personal integrity of the participants. Therefore, we put in several precautionary steps including: 1) only obtaining the data in pseudonymised form, 2) storing the data in a secure server, 3) only giving access to the researcher(s) doing the actual analysis after data security training. From the ‘autonomy’ perspective, ideally, the participants should have been able to decide to be included in the study or not. However, currently, there is no option to opt out from the administrative registers. At the same time, we do not have the means to identify, contact, and obtain informed consent directly from the participants, given that we were only given the pseudonymised dataset without the possibility of tracing the participants and such efforts would require enormous resources. In relation to the ‘justice’ principle, our studies were limited to only certain groups in the population, i.e., people who have personal identification numbers (to be included in the registers). Therefore, our studies have excluded some of the most vulnerable people in the society, i.e., refugees; and our study results might not be generalisable to these populations.

CAPRI have been recognised as a vulnerable population (189), but we have very limited knowledge about their needs in order to support them. This project is an effort to improve their situation. The use of registers minimises the direct harm for the study participants while at the same time ensuring adequate power to properly conduct the study analysis. Considering the benefits that might be gained and efforts that have been put in place to minimise the risk, we might conclude that the benefits outweigh the risk in this study.

## 5 RESULTS

### 5.1 PREVALENCE (STUDY I)

Overall, 9.5% of children and adolescents (0-17 years) in Sweden in 2006-2016 had at least one parent diagnosed with mental illness within secondary care. Slightly more had mothers diagnosed with mental illness (5.9%) compared to fathers (4.3%). However, for certain types of diagnosis, such as alcohol and drug misuse, the prevalence was higher for paternal (alcohol: 0.8%, drug: 0.5%) compared to maternal exposure (alcohol: 0.4%, drug: 0.3%). The highest prevalence was observed for CAPRI with parental common mental disorders, such as depressive (maternal: 2.5%, paternal: 1.5%) and anxiety disorders (maternal: 3.7%, paternal 2.2%). The lowest prevalence was observed for CAPRI with parental eating disorder (maternal: 0.2%) and non-affective psychotic disorder (maternal: 0.2%, paternal 0.2%). The prevalence of CAPRI increased by age of the young person, with the youngest (0-2 years) having the lowest proportion of parental mental illness and the oldest (15-17 years) having the highest proportion (Figure 5.1). The prevalence also increased by calendar period, with the lowest prevalence observed in the earlier period (2006-2009), and the highest observed in the later period (2013-2016, Figure 5.2).

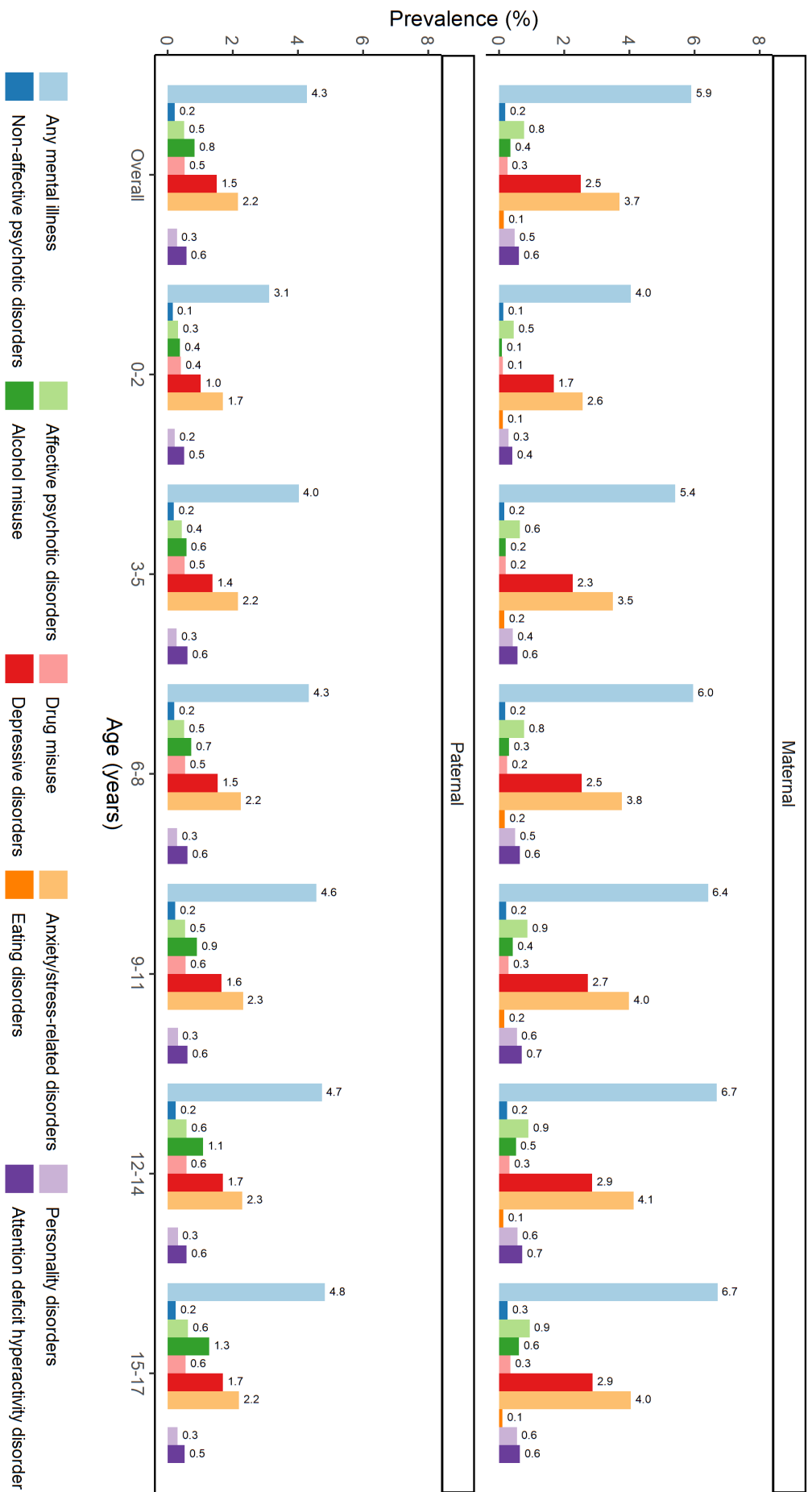


Figure 5.1 Period prevalence of children and adolescents with maternal and paternal mental illness, overall and by age group during 2006-2016

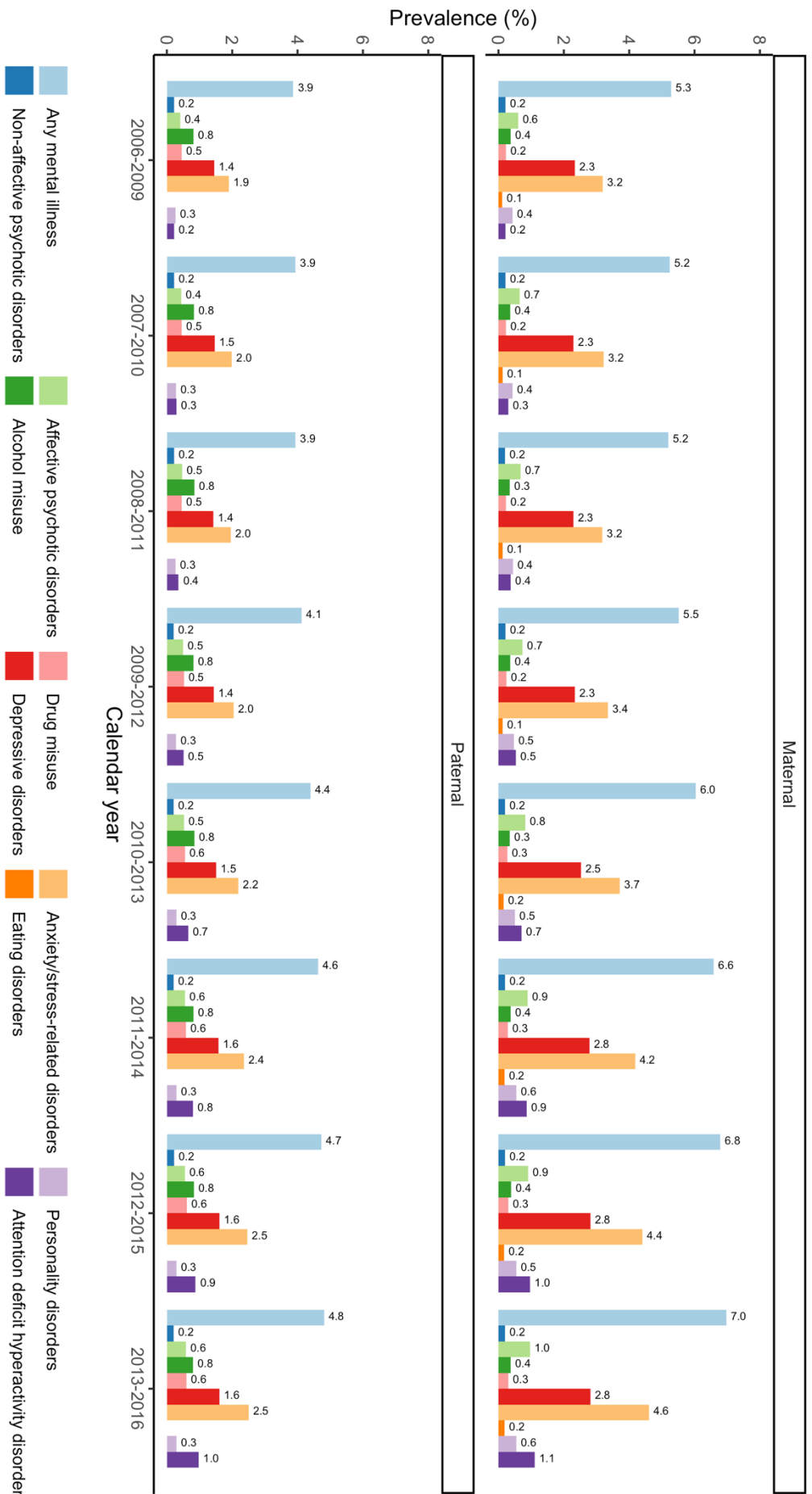


Figure 5.2 Period prevalence of children and adolescents with maternal and paternal mental illness by calendar period during 2006-2016



## 5.2 INJURY (STUDY II)

CAPRI had higher rates of injuries compared to children without parental mental illness and the differences were higher among the youngest age group (rate difference 0-1 year: 2,088/100,000 person-years, 15-17 years: 422/100,000 person-years, Figure 5.3).

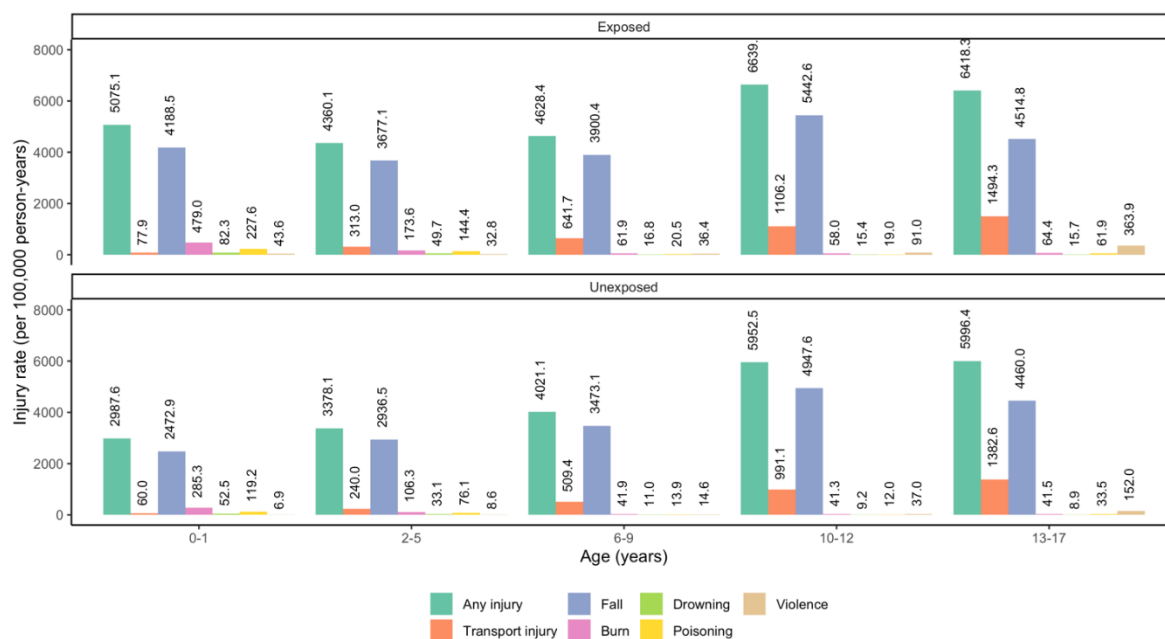


Figure 5.3 Injury rate (number of injuries per 100,000 person-years by age of the child and exposure to any parental mental illness

Adjusted rate ratios (RR) for the associations between any parental mental illness and any type of injury ranged from 1.30 (95% CI 1.26-1.33) in the youngest age group (0-1 year) to 1.06 (95% CI 1.04-1.08) in the oldest age group (15-17 years, Figure 5.4). Slightly higher RR was observed among CAPRI exposed to parental common mental disorders (e.g., RR depressive disorders 0-1 year 1.35, 95% CI 1.29-1.41) compared to more serious mental illness (e.g., RR non-affective psychotic disorders 0-1 year 1.06, 95% CI 0.91-1.24, Figure 5.4). Slightly higher RR was also observed among CAPRI with maternal (RR 0-1 year 1.31, 1.26-1.35) compared to paternal exposure (RR 0-1 year 1.27, 95% CI 1.21-1.33, Figure 5.4). The RR was relatively higher for the rarer type of injuries (e.g., RR violence 0-1 year 3.54, 95% CI 2.28-5.48), compared to more common injuries (e.g., RR fall 0-1 year 1.28, 95% CI 1.24-1.32, Figure 5.4).

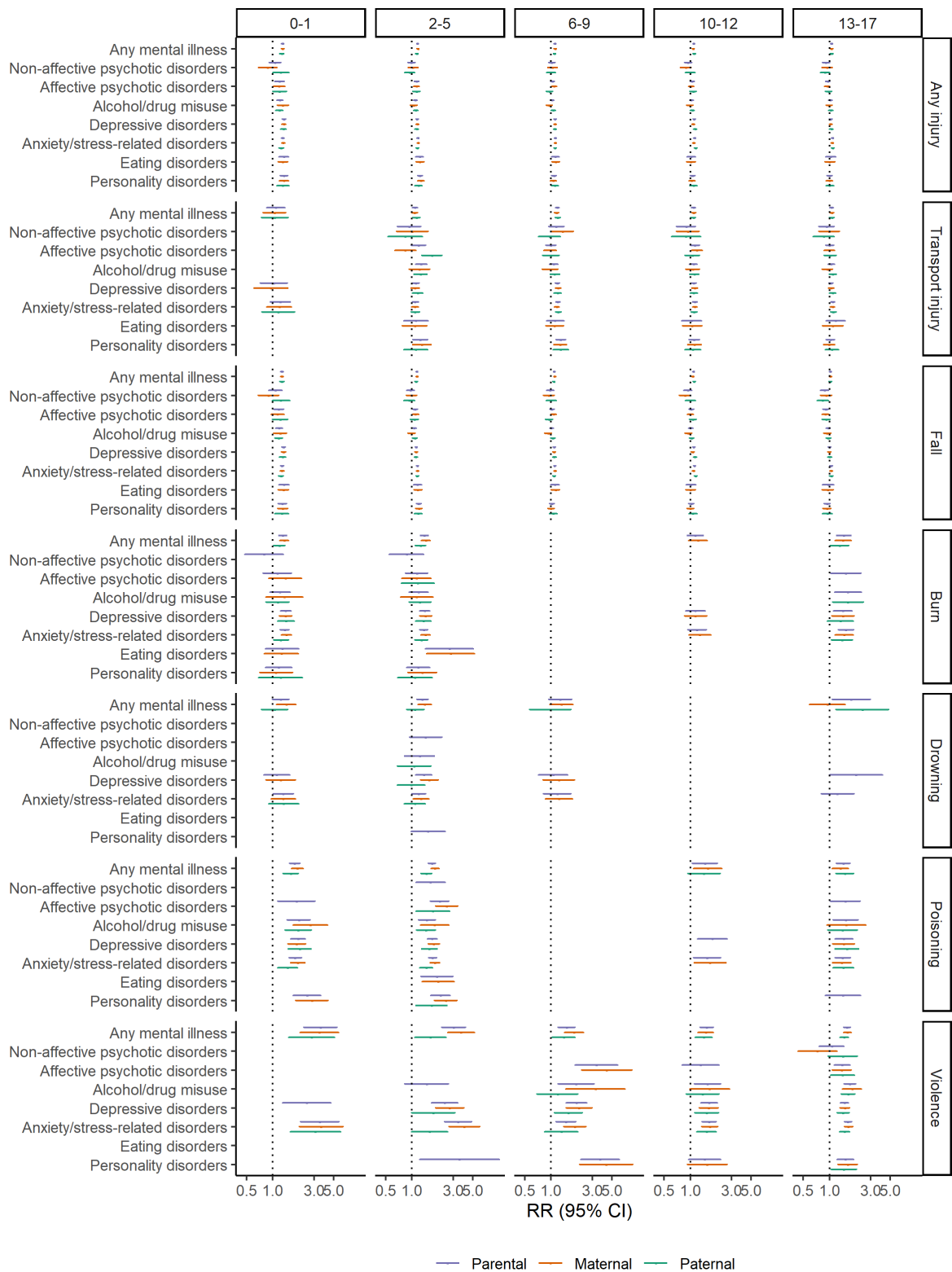


Figure 5.4 Rate ratios and 95% confidence interval for the associations between parental mental illness and offspring injuries. Adjusted for sex, birth year, the number of siblings, parental country of birth, parental age, living arrangements, parental education, parental employment, and household disposable income. Estimates with a low number of observations (<50 cases) were not presented.

### 5.3 AUTOIMMUNE DISEASE (STUDY III)

CAPRI had a slightly higher incidence for autoimmune disease (incidence rate: 218.6/100,000 person-years) compared to unexposed offspring (incidence rate: 172.9/100,000 person-years). Overall, after adjusting for potential confounders, exposure to parental mental illness was associated with a slightly higher risk for autoimmune diseases (adjusted HR 1.05, 95% CI 1.02-1.08, Figure 5.5) and the increase in risk was only slightly higher for maternal (HR 1.06, 95% CI 1.03-1.10), compared to paternal exposure (HR 1.04, 95% CI 1.00-1.08). For the majority of associations between individual mental illness and autoimmune disease, there was little evidence of an association (Figure 5.5). Nonetheless, some associations were worth noting. Exposure to parental common mental disorders (depressive or anxiety disorders), was associated with an increase in the risk of psoriasis, JIA, and inflammatory bowel disease (Figure 5.5). Maternal eating disorder was associated with up to 40% increase in risk for type 1 diabetes in the offspring (HR 1.41, 95% CI 1.05-1.89, Figure 5.5) and paternal depressive disorders were associated with an 18% increase in risk for psoriasis (HR 1.18, 95% CI 1.04-1.34, Figure 5.5). On the other hand, maternal non-affective psychotic disorder was associated with a decrease in risk of coeliac disease (HR 0.68, 95% CI 0.49-0.95), while paternal alcohol/drug misuse was associated with a decrease in risk of inflammatory bowel disease (HR 0.80, 95% CI 0.64-0.99).

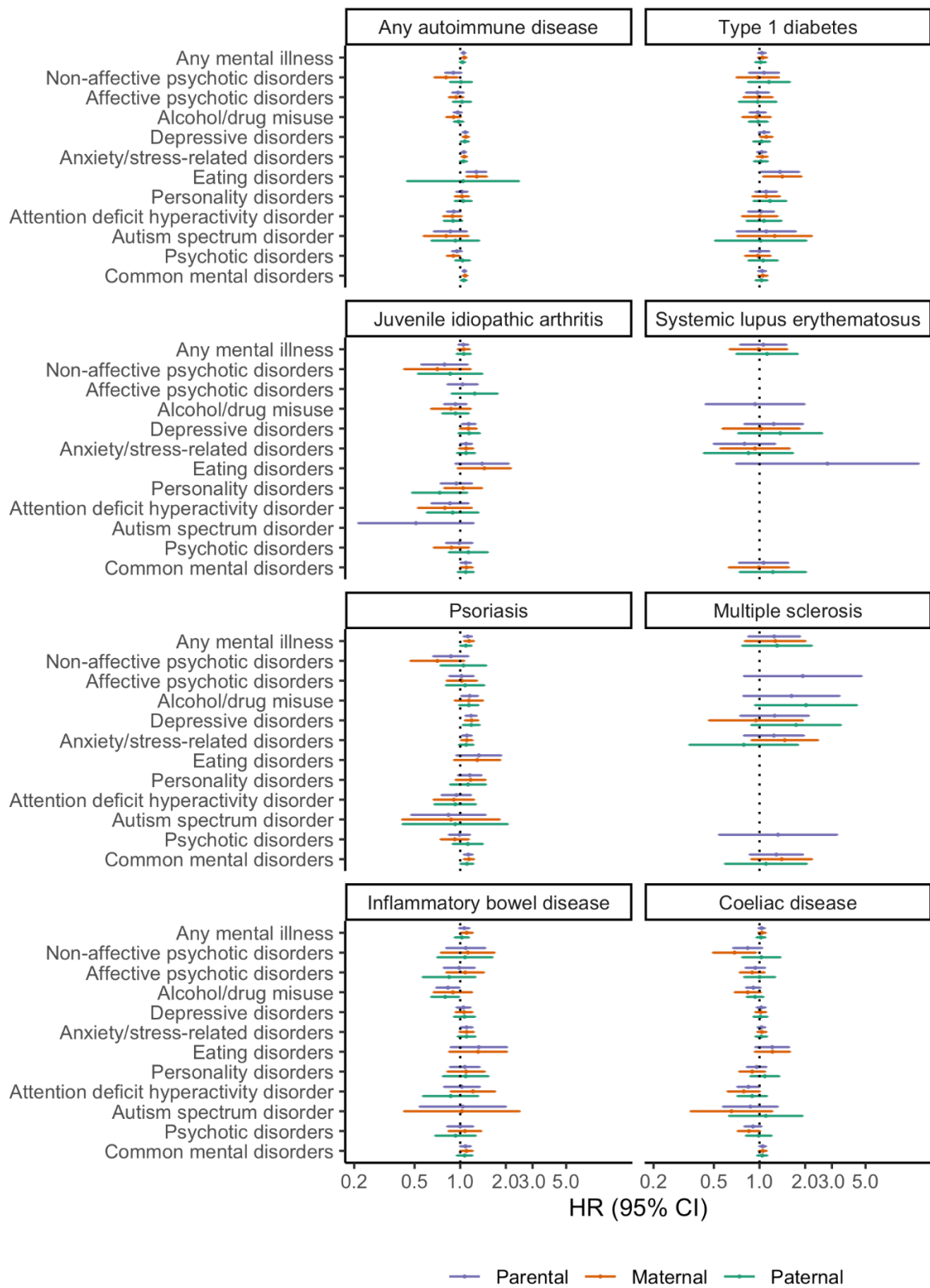


Figure 5.5 Hazard ratios and 95% confidence intervals for the association between parental mental illness and autoimmune diseases among the children. Adjusted for birth year, parental age, parental country of birth, parental education, household disposable income, and parental history of autoimmune disease. Estimates with a low number of observations (<5 cases) were not presented.

Sensitivity analyses using at least 2 registered autoimmune disease diagnoses (Figure 5.6) and using only exposure at birth (Figure 5.7) produced largely similar results although some of the estimates were attenuated. However, exposure to paternal alcohol/drug misuse diagnosed before birth was associated with an increase in the risk of inflammatory bowel disease (HR 1.10, 95% CI 0.82-1.48, Figure 5.7), albeit with wide confidence intervals, in contrast to the decrease observed in the main analysis.

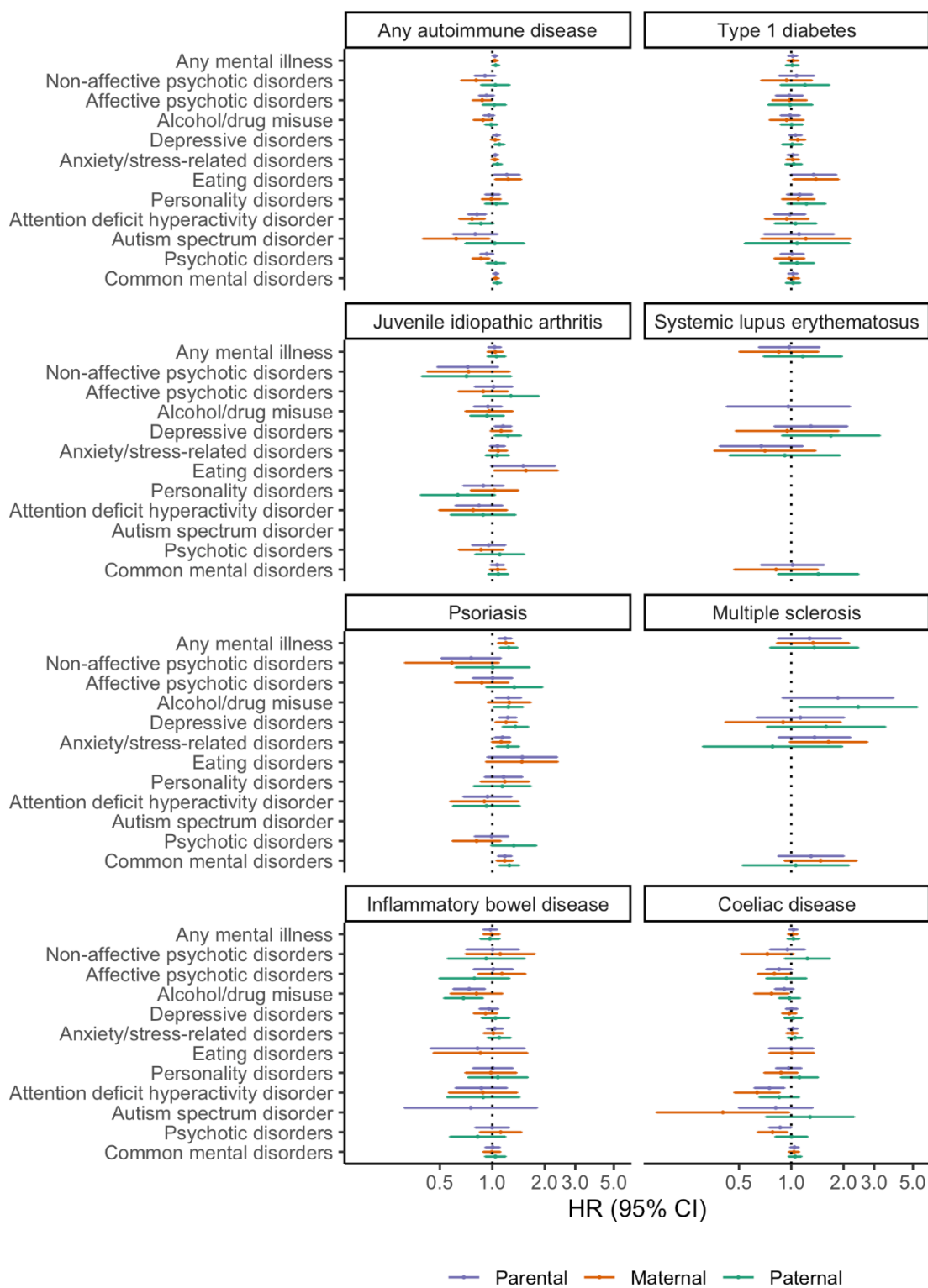


Figure 5.6 Hazard ratios and 95% confidence intervals for the association between parental mental illness and autoimmune diseases among the children, sensitivity analysis with at least 2 registered autoimmune disease diagnoses. Adjusted for birth year, parental age, parental country of birth, parental education, household disposable income, and parental history of autoimmune disease. Estimates with a low number of observations (<5 cases) were not presented.

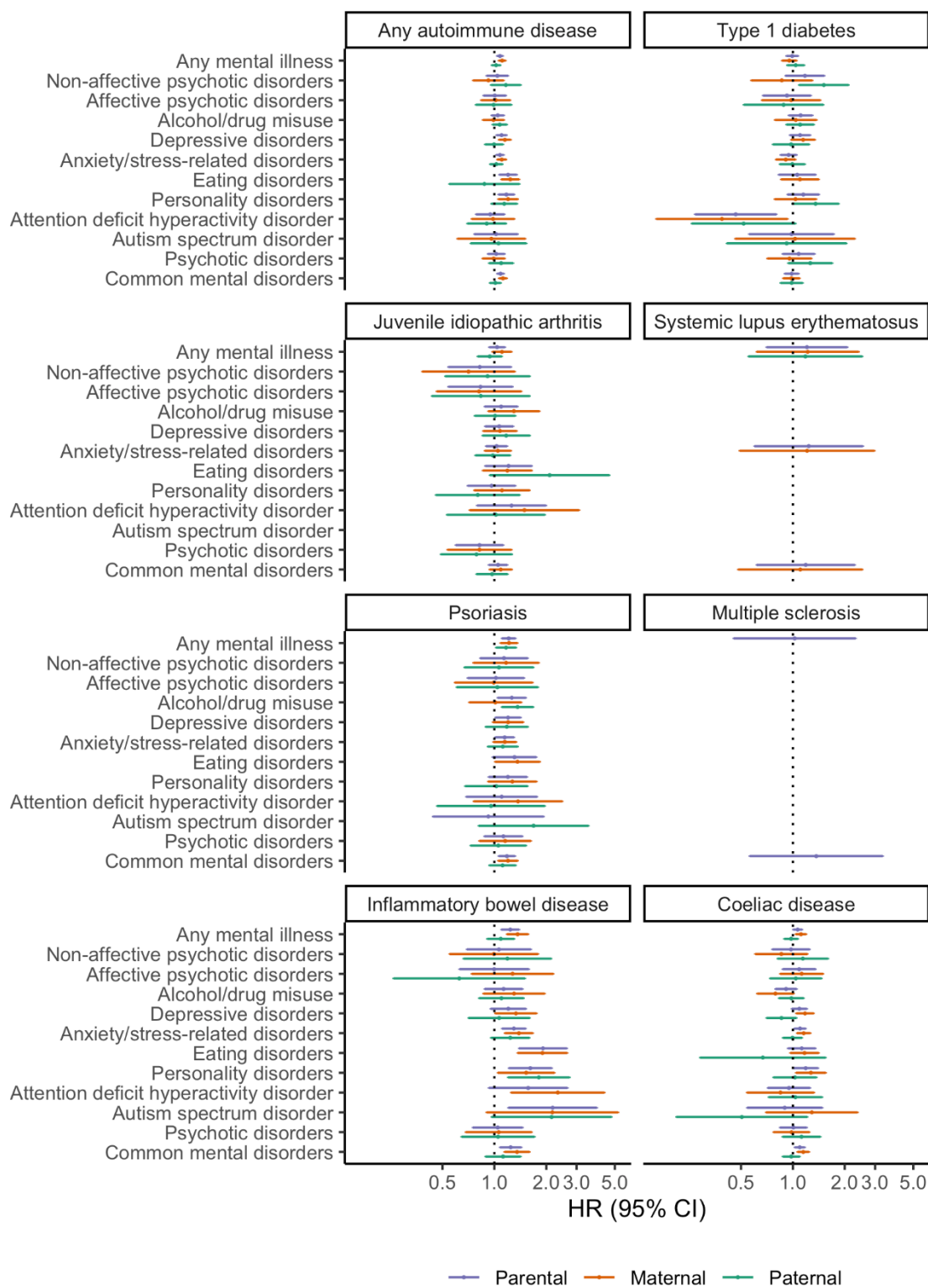


Figure 5.7 Hazard ratios and 95% confidence intervals for the association between parental mental illness and autoimmune diseases among the children, sensitivity analysis with exposure measured prior to childbirth. Adjusted for birth year, parental age, parental country of birth, parental education, household disposable income, and parental history of autoimmune disease. Estimates with a low number of observations (<5 cases) were not presented.

## 5.4 CANCER (STUDY IV)

In Sweden, CAPRI had a slightly lower incidence of cancer overall, compared to children without parental mental illness (incidence rate maternal exposed vs unexposed: 17.6 vs 18.2/100,000 person-years; paternal exposed vs unexposed 15.7 vs 18.3/100,000 person-years). On the other hand, in England, CAPRI exposed to maternal mental illness had a slightly higher incidence of cancer (incidence rate exposed vs unexposed 16.4 vs 15.2/100,000 person-years).

Results from pooled data analysis showed that exposure to maternal mental illness (except for maternal psychotic disorder) was associated with a 6-32% increase in the risk of childhood cancer, although all of the credible intervals (CrI) included 1, indicating uncertainty in the estimates, i.e., we cannot rule out a potential decrease in the risk (Table 5.1). In contrast, maternal psychotic disorder was associated with a decrease in risk of cancer among offspring, although the CrI also included 1, meaning we cannot rule out an increased risk (HR 0.74, 95% CrI 0.44-1.21). On the other hand, exposure to paternal psychotic disorder was potentially associated with an increase in the risk of cancer, (HR 1.20, 95% CI 0.82-1.75), whereas exposure to paternal common mental disorder and other mental illness might be associated with a 15% decrease in risk of childhood cancer, although there was also uncertainty within all these estimates, i.e., we cannot rule out potential associations in the opposite directions (Table 5.1).

Table 5.1 Association between maternal and paternal mental illness and childhood cancer

Mental illness	Maternal	England	Pooled	Paternal
	Sweden Adjusted HR (95% CI) <sup>a</sup>	Adjusted HR (95% CI) <sup>b</sup>	HR (95%CrI) <sup>c</sup>	Sweden Adjusted HR (95% CI) <sup>a</sup>
Any mental illness	1.02 (0.90-1.15)	1.10 (0.95-1.27)	1.06 (0.83-1.34)	0.94 (0.81-1.10)
Psychotic disorders	0.80 (0.56-1.17)	0.39 (0.10-1.55)	0.74 (0.44-1.21)	1.20 (0.82-1.75)
Alcohol/drug misuse	1.21 (0.86-1.71)	1.58 (0.91-2.76)	1.32 (0.89-1.98)	1.02 (0.79-1.32)
Common mental disorders	1.02 (0.90-1.16)	1.10 (0.95-1.28)	1.06 (0.83-1.35)	0.85 (0.71-1.02)
Other mental illness	1.28 (0.95-1.73)	0.85 (0.41-1.76)	1.18 (0.76-1.76)	0.87 (0.53-1.44)

<sup>a</sup>Adjusted for child's sex, birth year, parental age, parental country of birth, parental education, household disposable income in quintiles, parental history of cancer, maternal comorbid common mental illness, maternal comorbid psychotic disorders, maternal comorbid other mental illness, paternal comorbid common mental illness, paternal comorbid psychotic disorders, paternal comorbid other mental illness.

<sup>b</sup>Adjusted for child's sex, child's ethnicity, maternal age, maternal smoking during child's life, antibiotic use during pregnancy, region, and simultaneously for other mental illness exposure.

<sup>c</sup>Using Bayesian random-effects meta-analysis with using half-normal distribution ( $\tau=0.2$ ) as heterogeneity prior

Changing the values for heterogeneity prior affected the width of the credible interval, with higher heterogeneity reflected in a wider confidence interval. However, the point estimates remained similar (Table 5.2).



Table 5.2 Pooled estimates for the associations between maternal mental illness and childhood cancer with different ranges of heterogeneity prior ( $\tau$ )

$\tau$	Any mental illness HR (95%CrI) <sup>a</sup>	Psychotic disorders HR (95%CrI) <sup>a</sup>	Alcohol/drug misuse HR (95%CrI) <sup>a</sup>	Common mental disorders HR (95%CrI) <sup>a</sup>	Other mental illness HR (95%CrI) <sup>a</sup>
0.01	1.05 (0.96-1.16)	0.76 (0.53-1.09)	1.30 (0.97-1.74)	1.05 (0.96-1.16)	1.21 (0.91-1.59)
0.05	1.05 (0.94-1.18)	0.76 (0.53-1.10)	1.31 (0.97-1.76)	1.05 (0.94-1.19)	1.20 (0.90-1.60)
0.1	1.05 (0.91-1.23)	0.76 (0.51-1.12)	1.31 (0.95-1.82)	1.05 (0.90-1.23)	1.19 (0.86-1.64)
0.2	1.06 (0.83-1.34)	0.74 (0.44-1.21)	1.32 (0.89-1.98)	1.06 (0.83-1.35)	1.18 (0.76-1.76)
0.5	1.06 (0.65-1.72)	0.71 (0.28-1.55)	1.33 (0.70-2.64)	1.06 (0.65-1.72)	1.15 (0.53-2.23)
1	1.06 (0.45-2.48)	0.69 (0.15-2.39)	1.34 (0.46-4.09)	1.06 (0.45-2.49)	1.14 (0.33-3.43)

<sup>a</sup>Hazard ratios and 95% credible interval obtained using Bayesian random-effects meta-analysis with using half-normal distribution as heterogeneity prior

## 5.5 SOCIOECONOMIC ADVERSITY (STUDY I)

CAPRI were more likely to experience socioeconomic adversity, including living in families which received social welfare benefits (OR paternal 5.99, 95% CI 5.89-6.08), living in a family within the lowest income quintiles (OR paternal 2.95, 95% CI 2.91-2.99), having parents who are unemployed (OR paternal 2.96, 95% CI 2.87-3.06), and not having parents with tertiary education (OR paternal 1.81, 95% CI 1.78-1.83). Moreover, these young people were also more likely to not live with their parents and to have parents who were teenagers at birth (Figure 5.8).

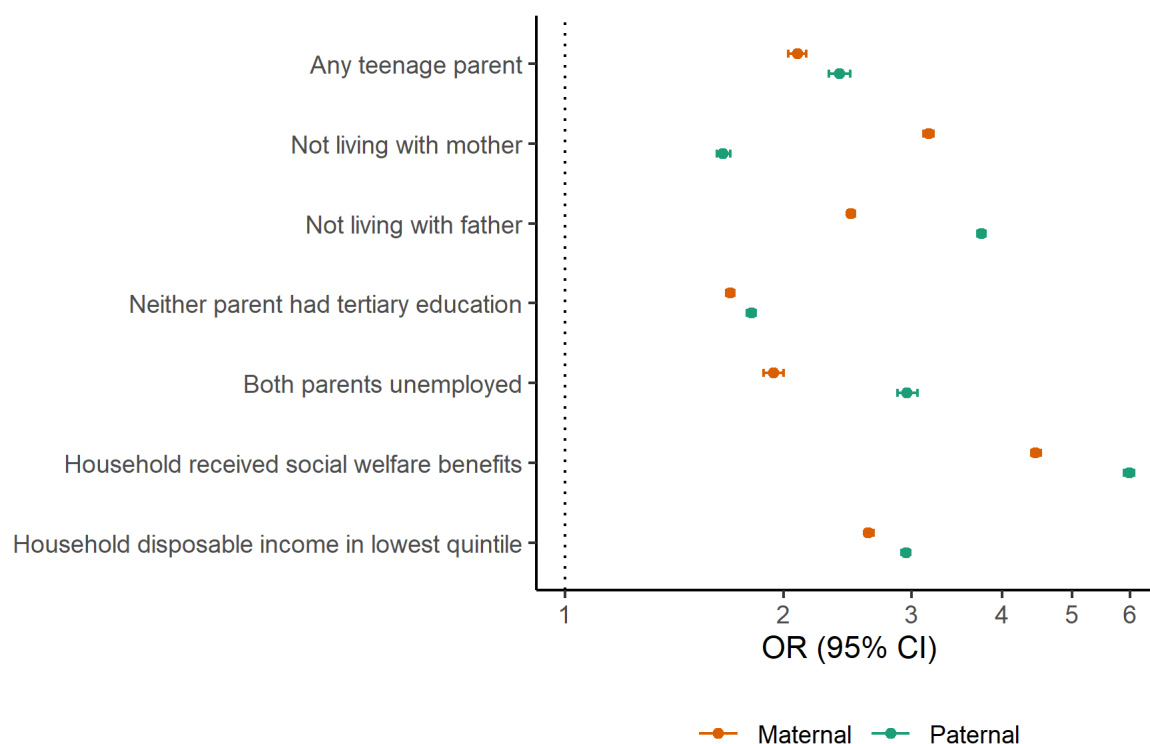


Figure 5.8 Odds ratios and 95% confidence interval for the associations between maternal and paternal mental illness and indicators of socioeconomic adversity. Adjusted for age group and year.

## **5.6 OUT-OF-HOME CARE PLACEMENT (STUDY V)**

CAPRI had a higher incidence of placement in out-of-home care, compared to those without parental mental illness (incidence rate 6.3 vs 0.8/1,000 person-years). Overall, CAPRI were more likely to be placed in out-of-home care (HR 4.42, 95% CI 4.24-4.61, Figure 5.9). Those with maternal mental illness were up to four times more likely to be placed in out-of-home care (95% CI 4.37-4.76), whereas those with paternal mental illness were up to two times more likely to be placed (95% CI 2.56-2.81, Figure 5.9). All mental illness diagnoses were associated with an increased likelihood of out-of-home care placement. However, parental intellectual disability, alcohol/drug misuse, and non-affective psychosis were among the diagnoses with the highest likelihood of placement (Figure 5.9). There was a variation in the likelihood of placement by age of children, with the highest HR of placement occurring during the first year of life (HR 0-1 year 5.77, 95% CI 5.42-6.14).

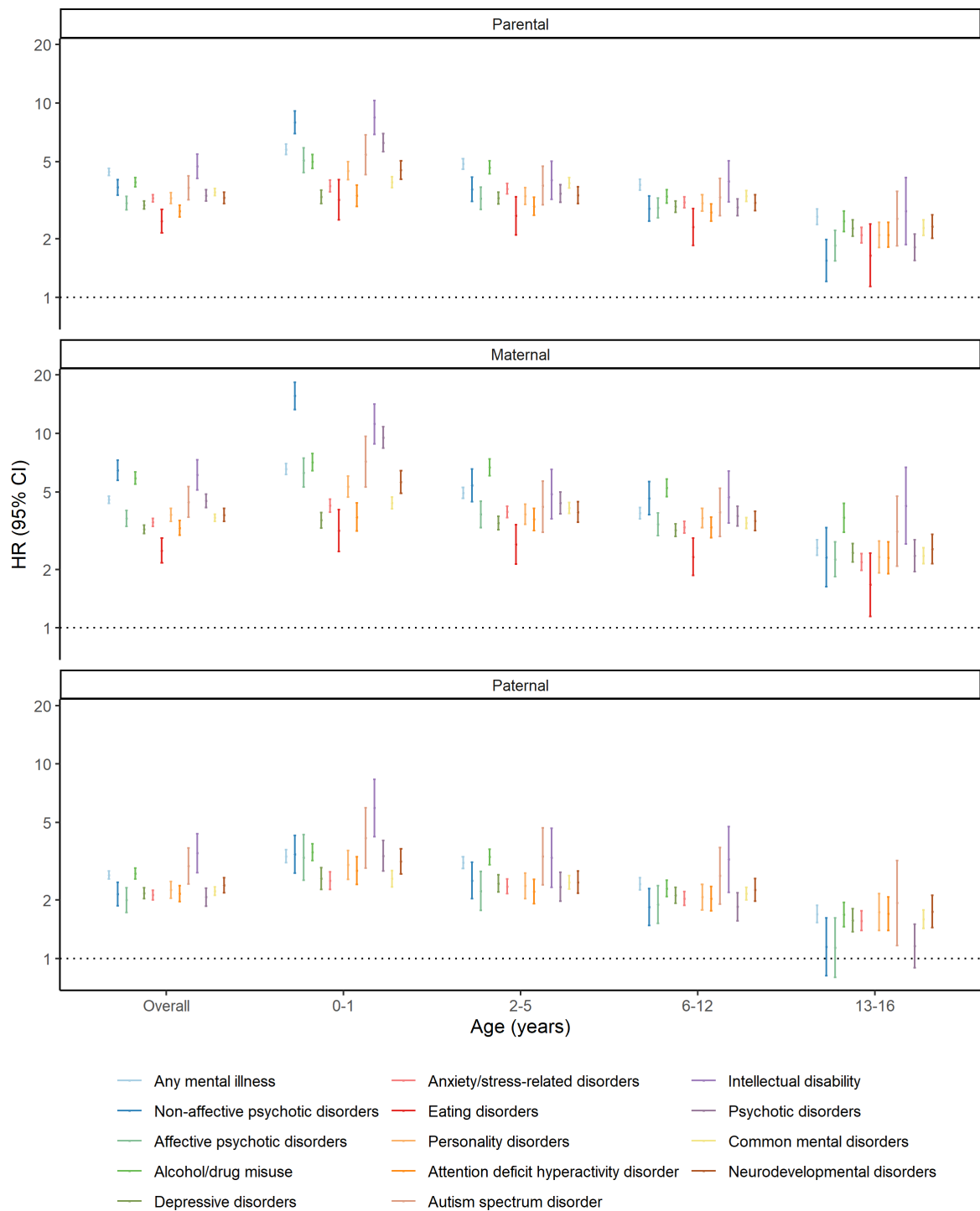


Figure 5.9 Hazard ratios and 95% confidence intervals for the association between parental mental illness and out-of-home care placement. Adjusted for sex, birth year, the number of siblings, parental age, parental country of birth, parental marital status, parental education, household receipt of social welfare benefits, household disposable income and parental history of out-of-home care placement. Estimates with a low number of observations (<10 cases) were not presented.

Various demographics and socioeconomic variables were found to modify the association between out-of-home care placement and parental mental illness. Children with parental mental illness who lived in lower socioeconomic positions had up to 15 times higher likelihood for placement compared to children without parental mental illness living in higher socioeconomic positions (Table 5.3).

Table 5.3 The associations between any parental mental illness<sup>a</sup> and risk of first out-of-home care placement across different strata of demographics, socioeconomic, other health characteristics

Variables	Categories	Parental mental illness		p-value <sup>c</sup>
		No HR (95% CI) <sup>b</sup>	Yes HR (95% CI) <sup>b</sup>	
<b>Demographics</b>				
Sex	Female	0.98 (0.94-1.02)	4.29 (4.08-4.52)	0.023
	Male	1.00	4.09 (3.88-4.31)	
Birth year	2000-2003	1.00	3.79 (3.58-4.01)	0.000
	2004-2007	0.91 (0.87-0.96)	3.94 (3.72-4.17)	
	2008-2011	0.78 (0.74-0.83)	3.82 (3.59-4.05)	
Number of siblings	0	1.00	3.52 (3.35-3.70)	0.000
	1	0.50 (0.47-0.53)	2.73 (2.57-2.90)	
	≥2	0.68 (0.64-0.73)	2.89 (2.67-3.12)	
Parental country of birth	All known parents born outside Sweden	1.43 (1.32-1.55)	4.33 (3.96-4.73)	0.000
	All known parents born in Sweden	1.00	5.21 (4.93-5.52)	
	One parent born outside and one parent born inside Sweden	1.58 (1.47-1.71)	6.14 (5.69-6.62)	
Maternal age at birth (years)	<20	2.03 (1.85-2.23)	4.27 (3.87-4.71)	0.000
	20-29	0.97 (0.92-1.03)	3.96 (3.72-4.22)	
	30-39	1.00	5.16 (4.85-5.49)	
	>40	1.53 (1.37-1.71)	7.20 (6.47-8.01)	
Paternal age at birth (years)	<20	2.18 (1.87-2.54)	4.57 (3.95-5.28)	0.000
	20-29	1.01 (0.95-1.07)	3.90 (3.64-4.17)	
	30-39	1.00	4.99 (4.70-5.30)	
	>40	1.89 (1.77-2.02)	7.52 (6.98-8.10)	
Parental marital status	Unmarried	1.30 (1.23-1.37)	4.90 (4.60-5.22)	0.000
	Married or cohabiting	1.00	5.15 (4.83-5.48)	
<b>Socioeconomic characteristics</b>				
Parental education	Compulsory	5.32 (4.85-5.83)	15.08 (13.75-16.54)	0.000
	Secondary	2.78 (2.58-2.99)	13.09 (12.10-14.17)	
	University	1.00	6.64 (6.06-7.28)	
Parental employment status	Unemployed	2.70 (2.52-2.89)	8.50 (7.95-9.10)	0.000
	Employed	1.00	5.39 (5.11-5.68)	
Household receipt of social welfare benefits	No	1.00	6.18 (5.85-6.53)	0.000
	Yes	3.99 (3.74-4.26)	11.96 (11.21-12.75)	
Household disposable income in quintiles	Q1 (lowest)	2.57 (2.29-2.89)	9.11 (8.08-10.26)	0.000
	Q2	1.95 (1.74-2.19)	8.42 (7.49-9.48)	
	Q3	1.63 (1.45-1.83)	8.48 (7.51-9.58)	
	Q4	1.19 (1.05-1.36)	7.49 (6.56-8.56)	
	Q5 (highest)	1.00	6.37 (5.53-7.33)	
<b>Health and other social characteristics</b>				
Childhood psychopathology during follow up	No	1.00	4.61 (4.41-4.81)	0.000
	Yes	5.97 (5.49-6.50)	10.79 (9.96-11.69)	
Parental history of out-of-home care	No	1.00	4.94 (4.72-5.18)	0.000
	Yes	3.86 (3.62-4.12)	10.52 (9.89-11.19)	

placement

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<sup>a</sup>Children were considered exposed to parental mental illness from the first date of (mental illness) diagnosis until the end of follow up

<sup>b</sup>Including all other variables in the table

<sup>c</sup>p-value for interaction

## 6 DISCUSSION

Using the rich information provided from Swedish national registers, and linking with that from the UK where applicable, we were able to study the outcomes of offspring exposed to a wide range of parental mental illness. In doing so, we were able to establish the prevalence of CAPRI living in Sweden today, as well as to explore a range of potential (physical) health and social outcomes that these young people might experience. How these findings fit into our existing knowledge will be discussed in the following section (6.1 “The findings of the thesis in the context”).

Despite the apparent advantages of using national registers as data sources in our studies, limitations still exist. This will be discussed further in section 6.2 “Methodological considerations”. The conclusion of this whole project will be presented in section 7, and potential implications of the findings will be discussed in section 8 “Points of perspectives”.

### 6.1 THE FINDINGS OF THE THESIS IN THE CONTEXT

#### 6.1.1 Prevalence of CAPRI

One in 10 children and adolescents in Sweden today is likely to have at least one parent diagnosed with mental illness in secondary care.

In Study I, we report that around one in 10 young people aged 0-17 in Sweden has at least one parent diagnosed with a mental illness in secondary care. These figures increase as the age of the children increases, from 1 in 15 for 0-3-year-olds to 1 in 9 for 15-17-year-olds. We observed that the proportion with maternal mental illness was higher compared to paternal mental illness, for all mental illness diagnoses, except for alcohol/drug misuse. We also noted a gradual increase in the proportion of CAPRI over the study period to 2016.

Our estimates were lower than those reported from Canada (23), the UK (20), and Australia (21,22). In this study, we only have information for mental illness diagnosed and treated within secondary care, which means that we could only capture a fraction, (potentially more severe cases) of all mental illness diagnoses. Indeed, around 40-80% of all mental illness cases were treated only within primary care (190,191). By contrast, previous studies used either population-based surveys (21–23) or primary care data (20), which might explain the higher prevalence among these populations.

Similar to findings in the UK study, we observed that the prevalence of CAPRI increased with the child’s age (20). We hypothesised that this might reflect the accumulation of

observed mental illness diagnoses among parents, either as a result of long-term illness or because of repeated illness episodes (192).

We observed that an estimated 30% more children in Sweden were exposed to maternal compared to paternal mental illness. A possible explanation for these findings is that men may be less likely than women to seek help when experiencing mental health problems, which might lead to fewer cases recorded in the registers (192,193). Indeed, one Swedish study found that men were less likely than women to seek mental health care even when they perceived a need for it, which might be partially caused by concerns about social stigma or negative perceptions of healthcare (193).

Our findings of increasing CAPRI throughout the study period are consistent with the findings of the recent UK study (20). While it might reflect a true increasing burden of mental illness in society, we hypothesised that it might also be because of increasing awareness about mental illness in society; and a lower threshold for seeking mental healthcare (192,194).

### **6.1.2 Physical health outcomes among CAPRI**

In Studies II-IV, we investigated the physical health outcomes among CAPRI, namely injury, autoimmune diseases, and cancer.

CAPRI have higher risk for injury compared to children without parental mental illness, especially during the first years of life.

In Study II, we observed a higher risk for injury among CAPRI compared to children without parental mental illness, and the increase was particularly evident during the child's first years of life. The risk is slightly higher for maternal compared to paternal exposure and for common mental disorders compared to more serious mental illness (e.g., psychotic disorders). The risk is also higher for rarer types of injury, e.g., violence-related injury and poisoning compared to more common injury, e.g., falls and transport injury.

This is by far the most comprehensive study on the risk of injury among children with parental mental illness, examining a wide range of parental mental illness and injury throughout the child's life up until 18 years of age. Nevertheless, the findings are largely in agreement with studies that preceded this study (44–48,54–61) and the ones after (10,49–52).

Similar to studies by Hope et al. (54) and Lyngsøe et al. (51), we observed that the increase in the risk of injury was higher among the youngest children. These patterns were more prominent for common mental disorders, such as depression, as these 2 studies demonstrated

(51,54). We did not observe similar distinct patterns by child age in particular for non-affective psychotic disorders. However, a study on maternal schizophrenia and risk of child injury (52) reported increasing risk with child age for unintentional injury but decreasing risk for violence-related injury. Differences in these patterns might be attributed to the low number of cases for this particular exposure and outcome within our data.

Higher observed risk among children exposed to maternal compared to paternal mental illness had been reported by two studies, one examining parental substance misuse (55) and another examining parental serious mental illness (10). However, a study on maternal and paternal depression (61) reported similar estimates for both exposures and the risk of injury. These apparent differences in the findings might be partially attributed to differences in the study population included in the three studies. The first two studies (10,55) included younger children (around 0-6 years), whereas the third study included school-age children up to grade 6 (61). Indeed, we observed in our study that the differences were more apparent for younger children. For example, the HR for injury for maternal and paternal depression in age 0-1 was 1.35 and 1.33, whereas, for age 6-9, it was 1.11 and 1.11, respectively.

When it comes to risk by types of injury, comparison with other studies was a bit challenging. This is because different studies might include different types of injury with different definitions. For example, most previous studies (10,56,59) defined injury types as fractures, burn, and poisoning, based on Chapter XIX of the ICD-10 codes or corresponding classification, whereas ours and another study (52) classified it based on the external causes of injury and intent (Chapter XX) of the ICD-10 codes. Of the three studies which classified the injury as fractures, burn, and poisoning (10,56,59), all of them observed that the risk of injury was higher for poisoning, despite slightly different exposures that were studied, i.e., depression (59), depression and anxiety (56), and serious mental illness including major depressive disorders (10). Our finding was in agreement with these studies, where we found that the risk of poisoning was higher relative to other types of injury, except violence-related injury. That we observed a relatively higher risk for violence-related injury compared to other unintentional injuries was confirmed by a study by Taylor et al. (52), where they observed a relatively higher risk for assault compared to accidental injury among children with maternal schizophrenia.

Overall, CAPRI have a small increase in risk of autoimmune disease, although the majority of parental mental disorders diagnoses did not convey additional risk.

In Study III, we found that CAPRI had a very small (5%) increase in the risk of autoimmune disease overall compared to children without parental mental illness. However, we found little evidence for specific diagnoses except for psoriasis, JIA, and inflammatory bowel disease among children with parental common mental disorders or alcohol/drug misuse, and



for type 1 diabetes among children with maternal depression and eating disorders. We also observed a lower risk for inflammatory bowel disease among children exposed to parental and, in particular, paternal alcohol/drug misuse, and coeliac disease among children with maternal non-affective psychotic disorders.

To the best of our knowledge, this is the first and largest study investigating the relationships between parental mental illness and paediatric autoimmune disease outcome among offspring. One of our findings is contrary to that of Benros et al. (86) who found a slight increase in the risk of coeliac disease among individuals with parents or siblings with schizophrenia. However, both of our confidence intervals were relatively wide so we might not be able to exclude the possibility of random variations in attributing these differences.

Overall, we did not find enough evidence on risk of cancer among CAPRI.

In Study IV, we did not find evidence of an association between exposure to parental mental illness and the risk of childhood cancer among the offspring. However, our results tentatively indicated that exposure to maternal, but not paternal, psychotic disorder might be associated with a lower risk of childhood cancer. We also found that exposure to both maternal and paternal alcohol/drug misuse might be associated with a slight increase in the risk of childhood cancer.

A prior study looking at the association between parental any serious mental illness (schizophrenia, bipolar disorders or depression) reported little evidence of association with risk of cancer in the offspring (25). However, in contrast to our study, they (25) reported cancer outcomes up to 30 years of age and did not separate between maternal or paternal mental illness and the diagnoses. We observed that there might be different patterns of associations depending on the exposure, for example in psychotic disorders, something that was not reported previously.

Our findings were in line with previous studies which found an increase in the risk of cancer associated with alcohol or substance use among parents (110–112). Although we used different kinds of exposure (diagnosed alcohol/substance misuse), our results still pointed towards the same direction, perhaps indicating consistency of the evidence. Nevertheless, the associations between alcohol or substance misuse and the risk of offspring cancer are complex. Some studies indicate a dose-response relationship with the amount of consumption and risk of offspring cancer; and there might be differences in the associations by type of offspring cancer (110,112), which we could not explore in our study.

### *6.1.2.1 Possible underlying mechanisms*

The overall higher absolute and relative risk of injury observed among CAPRI (compared to children without parental mental illness) could be attributed to many different factors. First, parental mental illness might make it more difficult for parents to maintain parental supervision, which is particularly important during the first years of life (195,196). Second, it is also possible that there are differences in the extent of safety measures implemented by parents with mental illness, compared to parents without, as suggested previously (197,198). Third, there is also a possibility of maltreatment occurring among the children, as studies have shown an excess risk of harm and injury-related mortality among CAPRI (147,199). However, it should be noted that: 1) violence is a relatively rare outcome, even among CAPRI, 2) individuals with mental illness might also be more likely to experience violence, including domestic violence (34,38,39), and 3) we did not have the information about who perpetrated the violence. Fourth, certain more sedative psychotropic medications used in the treatment of especially serious mental illness, such as benzodiazepines, were previously associated with increased risk of injuries (200,201); thus, the excess risk that was observed here might be partially attributed to such treatment. However, to the best of our knowledge, no known studies have specifically assessed this possibility. Finally, higher structural disadvantages, i.e., socioeconomic adversity, which were common among families with parental mental illness might play a role in influencing the risk of injury among these children. For example, these families might not be able to afford additional safety measures for the home environment or might live in riskier areas for injury.

When it comes to the associations between parental mental illness and the risk of autoimmune diseases, there might be several possible explanations for the findings. First, shared genetics between certain mental disorders and certain autoimmune diseases might contribute to the observed associations. For example, previous work reported correlations between risk alleles for certain mental illnesses and autoimmune diseases, e.g., major depressive disorders and psoriasis and anorexia nervosa and type 1 diabetes – although these are not statistically significant (202). Another study identified a significant locus for anorexia nervosa, which has also been associated with type 1 diabetes (203). Second, both mental illness and autoimmune disease might share similar pathophysiology, possibly through inflammatory pathways (87,204). For example, changes in serum inflammatory markers, such as corticotropin-releasing hormone and C-reactive protein have been identified in both psoriasis and anxiety or depression. Third, certain mental illnesses might alter gut microbiota and influence the regulation of the immune system (205), which could manifest as later autoimmune diseases. However, how the second and third hypothetical mechanisms might translate into parents' transmission of this risk to their offspring needs further study. The fetal environment might play a role, through the effect of maternal mental illness on fetal development (15,206) which, in turn, may influence fetal environment and development of autoimmune disease in the offspring (207).

Apart from these potential biological mechanisms, other explanations might include differences in healthcare-seeking behaviours between mothers and fathers with and without

mental illness (208,209). Despite our efforts to control for relevant confounders, residual confounding is still likely to exist and materially influence the observed associations.

Similar to autoimmune diseases, studies have indicated possible shared genetic mechanisms between the aetiology of mental illness and cancer, particularly for schizophrenia (210–212). However, differences in the association between maternal and paternal psychotic disorders and risk of childhood cancer might indicate that other factors beyond the gene might also play a role, for example, fetal environment (213). Additionally, certain medications used to treat psychotic disorders have been suggested to have anti-cancer properties (214), which might partially explain the lower risk of cancer among offspring. However, the exact mechanisms still need to be elucidated in future studies. In the case of alcohol/drug misuse, it has been suggested that the observed increase in risk for offspring cancers might be attributed to teratogenic effects of misused substances (110,111), which might contribute to later cancer development in exposed offspring. Importantly, we cannot exclude potential residual confounding in all the observed associations.

### **6.1.3 Social outcomes among CAPRI**

We investigated the social outcomes among CAPRI in Study I (socioeconomic adversity) and Study V (out-of-home care placement).

CAPRI were up to six times more likely to experience a range of socioeconomic adversity.

We found that CAPRI were up to six times more likely to experience a range of socioeconomic adversities, including having parents with lower education, unemployed parents, living in the household that received social welfare benefits, or in a household with the lowest income quintiles in Study I. These young people were also more likely to have parents who were teenagers at birth and not to live with their parents.

Our findings are in line with a previous US study that reported a higher proportion of socioeconomic disadvantage among parents with mental illness (114). They are consistent with a previous Danish register study which found that children of parents with mental illness were less likely to live with the parents as they grew up (122). However, in contrast to the Danish study, we did not measure family dissolution at follow up (i.e., children stopped living with both parents) and, instead, used a cross-sectional picture of the living arrangements (measured at one point in time). Nevertheless, all of our findings suggested that regardless of the differences in the welfare system between the countries, socioeconomic adversity remains more prevalent among families with parental mental illness.

Overall, CAPRI were up to four times more likely to be placed in out-of-home care.

In Study V, we found that children with parental mental illness had an overall 4.4-fold increase in their likelihood to be placed in out-of-home care compared to children without parental mental illness. These children had a particularly higher likelihood to be placed in out-of-home care during infancy (0-1 year) compared to other age periods, and when the mothers experienced mental illness, compared to when the fathers did. While all parental diagnoses were associated with a higher likelihood for out-of-home care placement, some diagnoses, such as intellectual disability, alcohol/drug misuse, and non-affective psychosis were associated with an even higher likelihood of placement, compared to other diagnoses. Living in families with lower socioeconomic positions, e.g., having parents with lower education or living in the household with social welfare benefits, or with other social disadvantages, e.g., a previous parental history of out-of-home care placement were shown to increase the likelihood of placement even more among children with parental mental illness.

Our findings were in line with previous studies that have shown an increased likelihood for placement among children with parental mental illness (141–149). A similar increase in placement likelihood among youngest children had been observed previously (142,145). The first years of life might be the most challenging period for new parents where the parenting demand is especially high, at the time when they are also in a more vulnerable position when it comes to mental health. On the other hand, this is also the period when healthcare systems might have monitored families most closely, which might also explain the higher likelihood observed within this period.

The majority of studies that looked at mothers and fathers or partners' mental illness found that the likelihood for placement is usually higher for maternal exposure (142,143), as was observed in our study. However, one study (146) reported contrasting results and reported a higher relative increase associated with partner's compared to mother's schizophrenia. This could potentially be attributed to the different reference groups used to compare mother and partner's exposure, with 'no psychiatric disorders' being used in the partner, but not the mother's comparison (146). Nevertheless, differences in the likelihood of being placed between mothers and fathers' exposure might be tied to differences in parenting expectations between men and women, i.e., when fathers were ill, mothers were expected more to fulfil the parenting role, whereas the opposite might not happen to the same degree.

When it comes to comparison by mental illness diagnoses, direct comparison with previous studies is challenging because studies that examined multiple diagnoses do not necessarily focus on the same diagnoses. Nevertheless, our findings were similar to a Canadian study (141) which reported a relatively higher risk for out-of-home care placement at birth if the

mothers were diagnosed with substance misuse disorder, schizophrenia, or developmental disability, compared to mothers with mood or anxiety disorders. A slight difference with our study was that they found that maternal substance misuse was associated with the highest risk for out-of-home placement, followed by schizophrenia and developmental disability (141), whereas we find non-affective psychosis (including schizophrenia) creates the highest risk for CAPRI followed by intellectual disability, and alcohol/drug misuse (for placement in 0-1 years). Differences in the risk by diagnosis might be linked to how different illness symptoms manifest in different individuals and influence parenting capacity. It is also possible that healthcare, and potentially social workers, perceived the risk (of harm to the children) associated with different diagnoses differently (147), which might later influence the decision to place the child in out-of-home care.

Our findings on the heightened likelihood of placement among children with parental mental illness with socioeconomic disadvantage accord with a previous Danish study (142). In general, they observed a further increase in placement likelihood within families with lower socioeconomic positions, including having parents with minimum education and disability pension (142). In Study I, we showed that parental mental illness and socioeconomic adversity often co-occur, and, in this study, we showed that such co-occurrence meant that the children were at an even higher likelihood of experiencing other potentially adverse social outcomes; in this case, out-of-home care. This might mean that parents with mental illness have difficulties in fulfilling the demands of parenting and this is exacerbated by living in circumstances with a lack of resources and poor social support.

## **6.2 METHODOLOGICAL CONSIDERATIONS**

All studies in this thesis used linkage between Swedish national registers (or UK registers). The availability of high-quality longitudinal data with long-term follow-up covering (virtually) the whole Swedish population enabled us to conduct numerous studies to answer a range of research questions, in this case, from health to social outcomes, with sufficient power to detect differences in relatively rare exposures and outcomes. We were also able to combine estimates from another setting, in this case, England, to additionally increase the statistical power in Study IV. Including a large, representative sample from population-based cohorts would mean that our findings might be applicable in other settings, particularly the ones with similar populations and access to healthcare and welfare systems. Sweden has universal healthcare, where access is free for children under 18 years and adults should only pay certain amounts annually (up to 1200 SEK for outpatient care as of 2022) (215), which means that selection bias due to financial access is expected to be minimal in our settings. Our studies also used clinical diagnoses with high validity (156,171–175,179–182) to determine the exposures and health outcomes, which would minimise potential measurement error. Additionally, we were able to control for various individual and contextual factors, for example, socioeconomic positions, to try to get as close as possible to the true estimates. Nevertheless, some methodological limitations are worth mentioning.

First, while population registers are supposed to include virtually the whole Swedish population, certain groups residing in Sweden are less represented: for example, asylum-seekers. This might mean that our findings are less generalisable to these populations. Second, we only included mental illness exposures and health outcomes severe enough to be diagnosed within secondary care. Although some outcomes, such as autoimmune diseases and cancer are more likely to be diagnosed and treated within secondary care, other diagnoses, such as common mental disorders, might be diagnosed only within the primary care, at least a proportion of it (190,191). It means that our findings could only be generalised to those diagnosed within secondary care, likely towards those with more severe illness. Third, while some studies have shown relatively high validity for diagnoses made within the NPR (156,171–174,179–182), it should be acknowledged that not all diagnoses have been validated and some degree of measurement error is expected. Some diseases might have been misclassified as other diseases before the correct diagnosis was made, for example in the case of certain autoimmune diseases where diagnosing process is often difficult and take time. Fourth, while we tried to obtain true estimates of the associations, including by controlling for a range of covariates, there are some contextual factors that we were not able to capture, making the potential causal explanation for some of the associations difficult. For example, in Studies II and V, we did not have information about parenting capacity, which potentially could have played a role in the exposure-outcome development. Apart from the contextual factors, we also did not have genetic information within our study, which might be particularly useful in informing potential causal explanations in Studies III and IV.

One question arising from our findings is whether there is a problem with multiple comparisons. Concerns about multiple comparisons include the potential for spurious associations when testing associations between multiple exposures and/or outcomes (216). Methods like Bonferroni correction (217,218) reduce such Type I errors (i.e., rejecting the null hypothesis when it is true). On the other hand, these conventional methods have relatively poor performance (217) and come at a cost of increasing Type II errors, which might be more of a concern in certain study settings (218). Additionally, such correction implied a universal null hypothesis, where all associations that we observed in our study were all due to random variations (218), which might not be the case in our studies. Moreover, the exposures and outcomes outlined in the studies were determined before performing the analysis based on the current state of knowledge. Ultimately, the choice to perform correction for multiple comparisons should be based on the research questions at hand (217). In the case of the presence of multiple associations in the same study, one suggested approach was to present the results from all associations examined, which we did in all our studies (217).



## 7 CONCLUSIONS

Based on findings from the studies in this thesis, I conclude that:

1. Around 9.5% of children under 18 years in Sweden have at least one parent diagnosed with mental illness in secondary care. The proportion of CAPRI increased by age of and by calendar year. For all types of mental illness, the proportion is higher for maternal compared to paternal mental illness, except for alcohol/drug misuse.
2. Exposure to parental mental illness was associated with an increased risk of childhood injury from birth to adolescence. The risk is higher during infancy (up to 30%) and decreased thereafter. The risk is slightly higher for more common mental disorders compared to psychotic disorders, for maternal compared to paternal exposure, and for rarer types of injury compared to the more common ones.
3. Exposure to parental mental illness was associated with a small, 5% increased risk of autoimmune diseases among the children overall. However, we did not find an increased risk for most individual diagnoses of parental mental illness and children's autoimmune diseases.
4. We did not find conclusive evidence of increased cancer risk among CAPRI compared to children without parental mental illness. However, there is an indication that exposure to maternal, but not paternal psychotic disorders, might be associated with a lower risk of childhood cancer.
5. CAPRI were more likely to experience a range of socioeconomic adversities, including having parents who were unemployed or living in the household that received social welfare benefits.
6. CAPRI were also up to four times more likely to be placed in out-of-home care, particularly during infancy. They were more likely to be placed if the mothers received the diagnoses (compared to the fathers), and if the parents received diagnoses of intellectual disability, alcohol/drug misuse, or non-affective psychotic disorders. Socioeconomic adversity might further increase such likelihood (up to 15 times among children experiencing both parental mental illness and socioeconomic adversity).





## **8 POINTS OF PERSPECTIVE**

### **8.1 IMPLICATIONS FOR POLICY AND PRACTICE**

The findings of this thesis have some important implications. We observed that, in today's Sweden, the likelihood of having at least one parent with a diagnosed mental illness is relatively common. This knowledge could help combat the stigma surrounding parenting and mental illness, and that the possibility of mental illness in parents is not unusual and becomes part of everyday life – not a problem merely of “a selected few” (219). Additionally, given the sizeable proportion of these populations, more attention might be needed from the stakeholders and policymakers, for example, to ensure that there are relevant policies in place that could help in improving the well-being of the families.

Within the clinical practice, family perspectives might be put forward when thinking about how to help individuals living with mental illness and their families. Within the Swedish healthcare services, e.g., within the psychiatric care unit, it might have been common to inquire about the presence of children under 18 years in the household. This could probably then be followed up with questions surrounding concerns they might have as parents. This also points to a need to provide tailored parenting support to these parents. Family-based therapy approaches might also be needed within the healthcare services, given that oftentimes, children are left out of the conversations surrounding their parents' conditions and how it might impact them (220). Collaborations between families, healthcare providers (for example within psychiatric clinics and child healthcare centres), and social services are also necessary. Collaborations between social services are particularly important, given that our findings also showed a high degree of co-occurrence between parental mental illness and socioeconomic adversity. Therefore, potential social safety nets for families with parental mental illness should be considered to ensure that the children receive adequate care and support throughout their upbringing.

### **8.2 IMPLICATIONS FOR RESEARCH**

At a population level, we observed that CAPRI have a higher risk for certain adverse health and social outcomes, such as injury, certain autoimmune diseases, and out-of-home care placement. From a research perspective, future studies should strive to find potential causes behind these associations. For example, in the case of injury, future research questions include: are there differences in parenting capacities and/or safety practices between parents with and without mental illness that mediate excess child injury? Could these factors be modified by interventions? Is there an association between psychotropic medication use among ill parents and risk of offspring injury? For autoimmune diseases, future research might focus on teasing apart potential genetic and environmental influences of apparent associations. Like the injury outcomes, for out-of-home care, future research might compare differences in parenting capacity between different parental mental diagnoses and ask

whether these explain differences in placement likelihood. Additionally, future studies might take account of other potential mediators, such as child maltreatment; and determine how much this could explain the associations.

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