From Institute of Environmental Medicine
Karolinska Institutet, Stockholm, Sweden

MENTAL DISORDERS AS RISK FACTORS, COMORBIDITIES, AND CONSEQUENCES OF CANCER

Qianwei Liu

刘黔伟

Karolinska Institutet

Stockholm 2022

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN 978-91-8016-735-2

Mental disorders as risk factors, comorbidities, and consequences of cancer

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Qianwei Liu

The thesis will be defended in public at lecture hall Samuelssonsalen, Tomtebodavägen 6, Karolinska Institutet, Solna, Sweden, on 30th September 2022, 9:00 am.

Principal Supervisor:
Professor Fang Fang
Karolinska Institutet
Institute of Environmental Medicine

Co-supervisor(s):
Professor Karin Ekström Smedby
Karolinska Institutet
Department of Medicine

Docent Therese Andersson
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Docent Patrik Magnusson
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Opponent:
Professor Mette Nørgaard
Aarhus University
Department of Clinical Epidemiology

Examination Board:
Docent Kyriaki Kosidou
Karolinska Institutet
Department of Global Public Health

Docent Aldana Rosso
Lund University
Department of Clinical Sciences

Docent Erik Domellöf
Umeå University
Department of Psychology

To the world

ABSTRACT

Cancer and mental disorders are both heterogenous groups of diseases and with substantial public health burden. Accumulating evidence has supported an elevated risk of mental disorders among patients with cancer. Different explanations might underlie the association of cancer with the subsequent risk of mental disorders, including cancer-related inflammation, cancer treatment, and psychological distress in relation to receiving a diagnosis of and being treated for a life-threatening disease. The association of mental disorders with the subsequent risk of cancer is on the other hand largely unclear, though several hypotheses have been proposed to support such an association, including chronic inflammation, dysregulation of neurotransmitters (e.g., monoamine), and altered activity of hypothalamic–pituitary–adrenal axis and neuroplasticity. This thesis work aimed therefore to understand the role of mental disorders on cancer, as risk factors, comorbidities, and consequences.

In Paper I, we assessed whether there was an association between clinical diagnosis of autism spectrum disorder (ASD) and risk of cancer. Based on the Swedish national population and health registers, we conducted a nationwide population-based cohort study during 1987-2016 and found an elevated risk of cancer at early life among individuals with ASD, compared with individuals without ASD. The risk elevation was predominantly ascribable to ASD with co-occurring intellectual disability (ID) and/or birth defects, whereas ASD without these comorbidities was not related to an elevated risk of cancer.

In Paper II, we examined the association between clinical diagnosis of ID and risk of cancer, based on a nationwide population-based cohort study during 1973-2016 using Swedish national population and health registers. We found an elevated risk of overall cancer and eleven subtypes of cancer in individuals with ID (age ≤43 years), compared with individuals free of ID. The risk elevation was more pronounced for syndromic ID and not likely attributable to familial confounding.

In Paper III, we estimated risk of psychiatric disorders and cardiovascular diseases among individuals undergoing a diagnostic work-up of potential hematological malignancy during 2005-2014, based on the Skåne Healthcare Register. We observed highly increased risks of

psychiatric disorders and cardiovascular diseases among individuals undergoing a diagnostic work-up of suspected hematological malignancy, irrespective of the ultimate diagnosis.

In Paper IV, we evaluated the relationship between precancer psychiatric disorders and risk of subsequent sepsis among individuals with cancer during 2006-2014, based on the Swedish Cancer Register. We found an association between precancer psychiatric disorders and elevated risk of sepsis among individuals with cancer, calling for expanded surveillance and prevention of sepsis among cancer patients with precancer psychiatric disorders.

In conclusion, Papers I and II showed that ID, as well as ASD when comorbid with ID and/or birth defect, were risk factors of cancer. Paper III showed that individuals undergoing diagnostic work-up of suspected hematological malignancy were at highly increased risks of psychiatric disorders and cardiovascular diseases, irrespective of the ultimate diagnosis. Paper IV showed that precancer psychiatric disorders were related to an elevated risk of sepsis subsequent to cancer diagnosis.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to in the content by their Roman numerals (I-IV).

I. **Liu Q**, Yin W, Meijsen JJ, Reichenberg A, Gådin JR, Schork AJ, Adami HO, Kolevzon A, Sandin S, Fang F. Cancer risk in individuals with autism spectrum disorder. Ann Oncol. 2022;33:713-719.

II. **Liu Q**, Adami HO, Reichenberg A, Kolevzon A, Fang F, Sandin S. Cancer risk in individuals with intellectual disability in Sweden: A population-based cohort study. PLoS Med. 2021;18:e1003840.

III. **Liu Q**, Andersson TM, Jöud A, Shen Q, Schelin ME, Magnusson PK, Smedby KE, Fang F. Cardiovascular diseases and psychiatric disorders during the diagnostic workup of suspected hematological malignancy. Clin Epidemiol. 2019;11:1025-1034.

IV. **Liu Q**, Song H, Andersson TM, Magnusson PKE, Zhu J, Smedby KE, Fang F. Psychiatric disorders are associated with increased risk of sepsis following a cancer diagnosis. Cancer Res. 2020;80:3436-3442.

CONTENTS

LIST OF ABBREVIATIONS

ALL	Acute lymphoid leukemia
AML	Acute myeloid leukemia
ASD	Autism spectrum disorder
BBB	Blood-brain barrier
CI	Confidence interval
CNS	Central nervous system
CRP	C-reactive protein
DNMT3A	DNA-methyltransferase 3A
ENCR	European Network of Cancer Registries
FIGO	International Federation of Gynecology and Obstetrics
GR	Glucocorticoids receptor
HR	Hazard ratio
ICD	International Codes of Diseases
ID	Intellectual disability
IDO	Indoleamine 2,3 dioxygenase
IQ	Intelligence quotient
IRR	Incidence rate ratio
KI	Karolinska Institutet
KYN	Kynurenine
LISA	Longitudinal integrated database for health insurance and labor market studies
MAOIs	Monoamine oxidase inhibitors
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PDGR	General Data Protection Regulation
PVN	Paraventricular nucleus
QUIN	Quinolinic acid
SHR	Skåne Healthcare Register
SSRIs	Selective serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants

1 INTRODUCTION

Cancer is among the leading causes of death globally. For instance, in 2022, there are expected to be 1,918,030 newly diagnosed cases and 609,360 deaths due to cancer in the United States[1]. Mental disorders are on the other hand a leading cause of disability in our society, with a lifetime prevalence of around 30% worldwide[2]. Living with cancer is highly stressful and might increase the risk of mental disorders among cancer patients[3]. Patients with cancer have indeed been shown to have a higher prevalence of mental disorders than general population[3,4]. The temporal pattern of the risk of mental disorders during the entire disease process of cancer has however rarely been assessed for patients with cancer. Similarly, the health consequences of mental disorders in comorbidity with cancer have not been fully explored. Finally, although a link between mental disorders and subsequent risk of cancer has been proposed and there are various hypotheses regarding the underlying mechanisms linking together mental disorders and a higher risk of cancer[5-7], epidemiological evidence is largely lacking in supporting such an association. This thesis attempted to improve and update the understanding of potential roles of mental disorders, as risk factors, comorbidities, or consequences, on cancer, based on epidemiological findings.

2 BACKGROUND

2.1 Bidirectional link between mental disorders and cancer

2.1.1 Mental disorders and subsequent risk of cancer

Although mental disorders have been indicated as potential risk factors for cancer since long, there is a lack of consensus on the association of mental disorders with future risk of cancer[8-14]. Further, as cancer and mental disorders are both heterogenous diseases, an association of interest may also exist between specific types of cancer and specific types of mental disorders, e.g., neurodevelopmental disorders. Individuals with neurodevelopmental disorders have a life-long need for support from society, increased risk of comorbid conditions, and a reduced life expectancy[15-17]. Down syndrome is shown to be related to elevated risk of acute megakaryoblastic leukemia and acute lymphoblastic leukemia[18,19]. Similarly, there is also evidence supporting a link between Williams syndrome and lymphoma[20,21]. However, previous studies have predominately focused on the association between syndromic neurodevelopmental disorders and risk of some types of cancer, especially hematological malignancies[22,23]. Only a few studies, to our knowledge, have investigated risk of overall cancer among individuals with neurodevelopmental disorders in general[24,25]. However, these studies[24,25] had usually relatively small sample size and short follow-up, leading to low statistical power in disclosing a real association, particularly for rare cancers.

2.1.2 Cancer and subsequent risk of mental disorders

A large body of evidence has demonstrated that survivors of cancer, including solid tumors as well as hematological malignancies, are at increased risk for mental disorders[3,4,26-29]. Previous studies have however mainly concentrated on mental disorders after diagnosis of cancer[3,4], during cancer treatment[30], or as long-term psychiatric outcomes among survivors of cancer[31]. Only a few studies focused on the time period before diagnosis of potential cancer. One study has however indeed shown an increased risk of mental disorders nearly one year prior to diagnosis of cancer and the increased risk persisted during many years after cancer diagnosis[32]. Since mental comorbidities are associated with adverse prognosis and ineligibility of curative treatment[33], prevention and intervention of mental comorbidities

during early phase (e.g., during the diagnostic work-up) might make patients have larger probability of receiving curative treatment.

2.2 Potential mechanisms of the bidirectional link

2.2.1 Mechanisms linking cancer to subsequent mental disorders

2.2.1.1 Psychological distress

Patients with cancer are known to experience high level of psychological distress. The diagnostic work-up of a potential malignancy, receiving the final cancer diagnosis, the invasive and intensive treatment, and the relapse of disease could be regarded as a series of stressful life events[34-39]. The process of diagnostic work-up includes typically primary healthcare visit due to onset of symptoms, referral to specialist visit, laboratory examination, imaging examination, biopsy, and other clinical evaluations. During these diagnostic procedures, patients may experience simultaneously symptoms of unknown causes, uncertainty of final diagnosis, adjustment toward a diagnosis of malignant disease, and the deliberate decision-making regarding treatment, which could all be highly stressful. As treatment of cancer is known to be generally intensive and sometimes life threatening, patients might additionally suffer from severe side effects of treatment and medical complications[35,40]. Finally, as the treatment effect varies from patient to patient, a lack of response to treatment, relapse and disease progression are ultimate challenging stressors for patients with cancer.

In summary, patients with cancer experience psychological distress both acutely (around diagnostic work-up and primary treatment) and chronically (after primary treatment and during the survivorship). Both acute and chronic psychological distress might lead to increased risk of mental disorders, such as depression and anxiety[41-43].

2.2.1.2 Biological mechanisms

Understanding psychiatric disorders among patients with cancer as merely an outcome of severe stress reaction might however also overlook the complicated biological mechanisms of

the underlying cancer itself. Patients with cancer tend to have a series of biological alternations, compared with individuals without such malignancy, which might be other explanations of an increased risk of mental disorders.

2.2.1.2.1 Inflammation

A large body of evidence has suggested that inflammation might play an important role in the pathophysiology of mental disorders[44-48], and several studies have shown increased levels of pro-inflammatory cytokines, such as TNF-α, IL-1 and IL-6, among patients with mental disorders[49-51]. Interestingly, some cytokines are state-related markers and increase during exacerbations of symptoms, while other markers tend to be constant over time[52,53]. Persistent increase of biomarkers supports the link between low-grade inflammation and risk of severe psychiatric disorders[54]. Recent studies have also reported elevated levels of C-reactive protein (CRP) among patients with mental disorders, such as schizophrenia, depression, and bipolar disorder[55-62].

Patients with cancer are known to have immune dysfunction as well as high risk of infection[63,64], which could lead to similar symptoms as those demonstrated in patients with psychiatric disorders[47]. There is also an overlap of other symptoms between cancer and psychiatric disorders (especially depression and anxiety), such as fatigue, sleep disturbance, loss of appetite, and weight decrease[65-69]. Such overlap might also be attributable to the fact that both diseases are related to alterations in immune responses. For instance, an increased level of serum IL-6, which has been shown among both patients with cancer and patients with depression, might lead to sleep disturbance[65].

There are several mechanisms for pro-inflammatory cytokines to enter the brain, including leakage of blood-brain barrier (BBB), activation of transport and endothelial cells, and relaying secondary cytokine signals[70]. Once pro-inflammatory cytokines access brain, crosstalk between cytokines and brain domains could further lead to pathophysiology related to depression, such as altered neurotransmitter metabolism, neural plasticity, and neuroendocrine function[70,71]. Investigation of the associations between mental disorders and chronic inflammation could contribute to the understanding of the link between cancer and the subsequent risk of mental disorders.

2.2.1.2.2 Monoamine hypothesis

The potential role of monoamine neurotransmitters, such as serotonin, noradrenaline, and dopamine, in the initiation and development of mental disorders, especially depression, has been studied since mid-20th century[66]. Such hypothesis is supported by successful application of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), which could increase concentration of monoamine neurotransmitters, among individuals with psychiatric disorders[66,72]. Monoamines might contribute to the link between cancer and mental disorders as abnormal levels of pro-inflammatory cytokines, like the ones elevated in cancer[70], are known to dysregulate monoamines through activation of the enzyme indoleamine 2,3 dioxygenase (IDO)[70]. Activation of IDO can in turn result in serotonin deprivation as well as production of neurotoxic metabolites through activation of kynurenine (KYN) pathways[71]. In microglia, KYN could then be converted to quinolinic acid (QUIN), which is associated with neural excitotoxicity in relation to depression, through promotion of glutamate release and induction of oxidative stress[70,71].

2.2.1.2.3 Hypothalamic–pituitary–adrenal axis

The hypothalamic–pituitary–adrenal (HPA) axis is known to be important in maintaining homeostasis. Hyperactivity of HPA axis, which is characterized by a combination of increased release of stress-related cortisol and damaged glucocorticoid receptor-mediated feedback inhibition[66], is known to be involved in stress-related mental disorders. As biological alterations in relation to cancer (such as changes in immune system and metabolic system) pose a threat to the homeostasis, the HPA axis might become hyperactive in response to such alterations[71,73]. In addition, increased levels of cytokines in the case of cancer could impair the negative feedback regulation of the HPA axis, through inhibition of glucocorticoids receptor (GR) in the paraventricular nucleus (PVN) of hippocampus and hypothalamus or alteration of GR expression[71,73].

2.2.1.2.4 Neuroplasticity

Neuroplasticity is the growth and adaptability of a neuron that can be regulated by inflammatory cytokines and HPA axis[74]. In physiological condition, cytokines such as IL-1,

IL-6 and TNF-α promote neurogenesis and support the development of neuron. In the setting of cancer, dysfunction of immune system and increased level of pro-inflammatory cytokines might result in impairment of neuroplasticity and reduction of neurogenesis in astrocytes and oligodendrocytes, through elevated glutamate release, oxidative stress, or induction of apoptosis[70,71].

2.2.1.3 Treatment of cancer

As advances in treatment have dramatically improved overall survival rate of individuals with cancer, there has been increasing interest on the psychological side effects or sequelae among survivors of cancer[75]. Treatment of cancer, such as chemotherapy, surgery, or radiotherapy, is known to be intensive or invasive, which might lead to severe emotional distress for cancer patients[30,76]. Different treatment strategies could induce risk of mental disorders to different extent[77,78]. There are several potential mechanisms underlying the increased risk of mental disorders associated with cancer treatment. One possible reason is the direct cerebellar and neurologic toxicity of intensive treatment[79,80]. Another potential mechanism is that treatment of cancer could impair periphery tissues. Damage of periphery tissues could increase release and production of inflammatory cytokines, perhaps inducing inflammation-related psychiatric disorders[71]. Another potential factor is that regimens of chemotherapy for cancer usually include glucocorticoids, which might induce abnormality and dysfunction of the HPA axis and therefore increase the risks of depression and suicide[81]. However, other studies found that glucocorticoids yielded anti-inflammatory effects and reduced risk of mental disorders[82,83]. The exact role of glucocorticoids in the link between treatment of cancer and mental disorders needs to be further explored.

2.2.2 Mechanisms linking mental disorders to subsequent cancer

2.2.2.1 Immune dysfunction of mental disorders

Amounting evidence supports that psychological distress could induce a series of biological changes, including immune dysfunction[5]. Such “stress-induced immune dysfunction” has been suggested to play a role in the tumorigenesis and participate in the process of both the initiation and progression of cancer[5,84,85], through regulating growth and survival of cancer cells by cellular events and cytokines including TNF-α, IL-1β, IL-23, and IL-6[84,85]. Elevated

serum levels of TNF-α and IL-6 have been further suggested to be associated with both the pathogenesis and prognosis of certain types of cancer[86-88].

2.2.2.2 Treatment of mental disorders

Previous research mainly focused on the association between antidepressants and cancer[89-91]. Laboratory data suggested that different antidepressant medications might have different impact on cancer[90,91]. For instance, sertraline, a type of selective serotonin reuptake inhibitors (SSRIs), has shown potential antiproliferative activity on multiple types of cancer both *in vivo* and *in vitro*[92], whereas the role of TCAs on the pathogenesis of cancer remains largely inconclusive, with both carcinogenic potential due to genotoxic activity and anticancer capability because of cytotoxic effect[93]. There are a few epidemiological studies that evaluated the association between psychiatric medications and risk of several types of cancer without however reaching a consensus[89,93-101]. Further studies are therefore needed to take into consideration the underlying indications of medication use and to elucidate the association between psychiatric medications and cancer risk.

2.2.3 Shared risk factors between cancer and mental disorders

In addition to the mechanisms discussed above, which could contribute to a specific direction of the link between cancer and mental disorders, there are also shared risk factors between cancer and mental disorders, which might also contribute to a greater-than-expected concurrence between these two groups of diseases.

2.2.3.1 Shared genetic and epigenetic risk factors

There may be shared genetic as well as epigenetic risk factors between several types of mental disorders and specific cancer types[102-105]. For instance, previous studies have demonstrated genetic correlations between psychiatric disorders, such as schizophrenia and depression, and breast cancer[102,103]. Candidate risk genes and related pathways of neurodevelopmental disorders, including autism and intellectual disability, have also been reported in cancer[104]. In addition, mutations in the epigenetic regulator DNA-

methyltransferase 3A (DNMT3A) were suggested to play a vital role in both cancer and specific types of autism, such as Tatton–Brown–Rahman syndrome[105].

2.2.3.2 Shared lifestyle risk factors

In addition to genetic and epigenetic risk factors, shared lifestyle risk factors might also play a role in the association between cancer and mental disorders. Although the etiologies of many cancer types and mental disorders are still largely unclear, epidemiological studies have identified several potentially shared lifestyle risk factors between these two groups of diseases, including obesity[106,107], diet pattern[108,109], tobacco smoking[110,111], and physical inactivity[112,113]. However, as some of these potential risk factors (e.g., tobacco smoking) might also be the consequence of mental disorders such as depression[114], there is a pressing need to verify the role of these factors, either as confounders or mediators, in the association between cancer and mental disorders.

3 RESEARCH AIMS

The primary aim of the thesis was to investigate the role of mental disorders on cancer, as risk factors, comorbidities, and consequences.

The specific research aims were:

Study I: To assess whether there is an association between ASD and risk of cancer.

Study II: To examine whether there is an association between ID and risk of cancer.

Study III: To estimate risks of psychiatric disorders and cardiovascular diseases during diagnostic work-up of suspected hematological malignancy.

Study IV: To evaluate the association between precancer psychiatric disorders and risk of sepsis following a cancer diagnosis.

4 MATERIALS AND METHODS

4.1 Study materials

4.1.1 Swedish population and health registers

4.1.1.1 Swedish Cancer Register

The Swedish Cancer Register was launched since 1958 to collect data, including clinical and pathological information, on all malignant cancers as well as certain types of benign tumors[115]. The diagnoses of cancer are coded according to the Swedish revisions of International Classification of Disease (ICD) systems. As healthcare providers are required to report all newly diagnosed malignancy to the Swedish Cancer Register by law, the completeness of the Swedish Cancer Register approaches 100%[115].

4.1.1.2 Swedish Patient Register

The Swedish Patient Register was set up to collect information on inpatient hospital visits from 1964 onward, and has reached 100% nationwide coverage since 1987[116]. The register started to collect data on outpatient visits since 2001, with around 80% coverage. All hospital diagnoses of diseases are coded according to the Swedish revisions of ICD codes (ICD-7 prior to 1969; ICD-8 1969-1986; ICD-9 1987-1996; ICD-10 from 1997 onward). The register is believed to be a reliable and valuable source for epidemiological research and diagnoses of various diseases have been proven to be valid in external validations[116].

4.1.1.3 Swedish Medical Birth Register

The Swedish Medical Birth Register was launched in 1973 to collect data on almost all deliveries in Sweden[117]. Information in the Swedish Medical Birth Register includes medical records from prenatal care (e.g., previous pregnancy and maternal smoking during pregnancy), delivery care (e.g., delivery mode), as well as neonatal care (e.g., birth weight, Apgar score at 1 minute/5 minutes/10 minutes, single birth/multiple births, and live birth/stillbirth)[117].

4.1.1.4 Other registers

The Swedish Total Population Register collects information on birth date, sex, immigration or emigration, residence, and so on[118]. The Cause of Death Register includes information on date and underlying (as well as contributory) causes of death[119]. The longitudinal integrated database for health insurance and Labor Market Studies (LISA) was established in 1990 to collect data on income, cohabitation status, employment, education, etc., for all individuals aged sixteen years or above residing in Sweden[120].The Swedish Multi-Generation Register contains information about familial links for all individuals born since 1932 in Sweden[121].

4.1.1.5 Skåne Healthcare Register

The Skåne Healthcare Register (SHR) compiles data of all levels of healthcare in the Skåne region[122], which is located at the most southern part of Sweden and has around 1.4 million residents. The SHR collects data on all levels of healthcare[122], including primary care and specialist care. From 1998 to 2017, the SHR collected data on a total of 143 million consultations, and the overwhelming preponderance of these have an assigned diagnosis[122].

4.1.2 Ascertainment of exposure and outcome

4.1.2.1 Ascertainment of cancer

Cancer cases were identified from the Swedish Cancer Register using the Swedish revisions of ICD-7 codes (Paper I and Paper II) or ICD-10 codes (Paper III and Paper IV). In Papers I, II and IV, we studied any cancer as well as several types of cancer. In Paper III, we focused on any hematological malignancy and subtypes of hematological malignancies. ICD-7 and ICD-10 codes used to identify the studied cancer types are listed in **Table 1** and **Table 2**, respectively. In Paper IV, we used information on cancer stage (available since 2004 in the Swedish Cancer Register) as a covariate in the analysis. We used the condensed TNM scheme of European Network of Cancer Registries (ENCR) in combination with the International Federation of Gynecology and Obstetrics (FIGO) to classify cancer stages (**Table 3**).

Table 1. ICD-7 codes for any cancer and subtypes of cancer

Cancer types	**ICD-7**
Any cancer	**140-209**
Oral	140-144
Salivary gland	142
Esophagus	150
Stomach	151
Small intestine	152
Colon	153
Rectum	154
Liver	155
Pancreas	157
Lung	162
Breast	170
Cervix	171
Uterus	172-174
Ovary	175
Testis	178
Kidney	180
Melanoma	190
Non-melanoma skin	191

Cancer types	**ICD-7**
Eye	192
Central nervous system (CNS)	193
Thyroid	194
Other endocrine gland	195
Bone	196
Connective tissue	197
Other or unspecified sites	199
Hodgkin's lymphoma	201
Non-Hodgkin's lymphoma	200, 202, 2041
Acute lymphoid leukemia (ALL)	2040, 2049
Acute myeloid leukemia (AML)	2050, 2059, 2060, 2069

This table is adapted from Liu Q et al. *Annals of Oncology*, 2022.[123]

Table 2. ICD-10 codes for any cancer and subtypes of cancer

Cancer types	**ICD 10**
Any cancer	**C00-C97, D45, D46, D471, D473**
CNS cancer	C70-C72
Breast cancer	C50
Colorectal cancer	C18-C20
Lung cancer	C34
Prostate cancer	C61
Non-melanoma skin cancer	C44
Hematological malignancy	C81-C96, D45, D46, D471, D473
Leukemia	C91-C95 (except for C911, C913, C914, C916)
Lymphoma	C81-C85, C88, C911, C913, C914, C916, C96
Myeloma	C90
Myelodysplastic syndrome	D46
Myeloproliferative neoplasm	D45, D471, D473
Others	All cancers except above

This table is adapted from Liu Q et al. *Clinical Epidemiology*, 2019[124] and Liu Q et al. *Cancer Research*, 2020[125].

Table 3. Cancer stage according to condensed TNM scheme and FIGO

Cancer stage	**TNM**			**FIGO**
	T	**N**	**M**	
Limited-stage localized	Localized	0	0	0 or I
Advanced-stage localized	Advanced	0	0	II
Regional spread	Any	+	0	III
Advanced	Any	Any	+	IV

4.1.2.2 Ascertainment of ASD, ID, psychiatric disorders, cardiovascular disease, and sepsis

In Paper I, we identified ASD cases (as exposure) from the Swedish Patient Register using the Swedish revisions of ICD-9 and ICD-10 codes. ASD cases were further classified into autistic disorder and other ASD. In Paper II, ID cases were also ascertained through the Swedish Patient Register as exposure using ICD-8, ICD-9, and ICD-10 codes. We further classified ID by severity (i.e., mild ID, moderate ID, severe ID, and profound, other, or unspecified ID) as well as type (i.e., idiopathic ID or syndromic ID). In Papers I and II, in addition to ascertainment of exposures, we also identified birth defects and congenital syndromes from the Patient Register. Psychiatric disorders and cardiovascular diseases (as outcomes) in Paper III and sepsis (as outcome) in Paper IV were identified from the SHR and Patient Register, respectively, using ICD-10 codes. ICD codes used to identify the exposures, outcomes, or comorbidities through the Swedish Patient Register are listed in **Table 4**.

Table 4. ICD codes for ASD (including subtype[a]), ID (including severity[b] and type[c]), birth defects, psychiatric disorders, cardiovascular disease, and sepsis

Diagnoses	**ICD-8**	**ICD-9**	**ICD-10**
ASD	NA	299A, 299B, 299X	F84.0, F84.5, F84.8, F84.9
Autistic disorder	NA	299A, 299B, 299X	F84.0
Other ASD	NA	NA	F84.5, F84.8, F84.9
Congenital malformations and chromosomal abnormalities (birth defects)	310.4-310.5, 311.4-311.5, 312.4-312.5, 313.4-313.5, 314.4-314.5, 315.4-315.5, and 740-759	740-759	Q00-Q99
ID	310-315	317, 318, 319	F70-F73, F78, F79
Mild ID (IQ[d]: 50-69)	310, 311	317	F70
Moderate ID (IQ: 35-49)	312	318A	F71
Severe ID (IQ: 20-34):	313	318B	F72
Profound ID (IQ: <20)	314	318C	F73
Unspecified or other ID	315	319	F78, F79

Psychiatric disorders[e]	-	-	F10-F99
Substance abuse	-	-	F10–F16/F18–F19
Depression	-	-	F32, F33
Anxiety	-	-	F40, F41
Stress reaction or adjustment disorder	-	-	F43
Somatoform/conversion disorder	-	-	F44–F45
Cardiovascular disease	-	-	I00-I99
Hypertension	-	-	I10, I11, I12, I13, I14, I15
Myocardial infarction	-	-	I21, I22
Embolism or thrombosis	-	-	I26, I74, I81, I82
Heart failure	-	-	I50
Stroke	-	-	I60, I61, I62, I63, I64

Sepsis	-	-	A02.1, A04.0-A04.3, A39–A41, A42.7, A48, A90–A99, B37.7, B38.7, B39.3, B40.7, B41.7, B42.7, B44.7, B45.7, B46.4, B95–B99, D65, and T80.2

[a] ASD subtype includes autistic disorder and other ASD (Asperger's syndrome, other pervasive developmental disorders, and unspecified pervasive developmental disorders).
[b] Borderline ID was included in mild ID.
[c] ID type was divided into syndromic ID and idiopathic ID, by etiology. Individuals with of ID and congenital malformations or chromosomal abnormalities were defined as syndromic ID. Individuals with ID but without congenital malformations or chromosomal abnormalities were defined as idiopathic ID.
[d] IQ is abbreviation of intelligence quotient.
[e] ICD codes for psychiatric disorders shown in above table are ICD-10 codes used in Papers III and IV. In Papers I and II, we aimed to control for parental history of psychiatric disorders as a covariate in the analysis and additionally included ICD codes of dementia. ICD codes of psychiatric disorders in Papers I and II include ICD-8 codes 290-315, ICD-9 codes 290-319, and ICD-10 codes F00-F99.
This table is adapted from Liu Q et al. *Annals of Oncology*, 2022[123], Liu Q et al. *PLOS Medicine*, 2021[126], Liu Q et al. *Clinical Epidemiology*, 2019[124] and Liu Q et al. *Cancer Research*, 2020[125].

4.2 Study design and methods

4.2.1 ASD and risk of cancer (Paper I)

4.2.1.1 Study design and participants

Based on the Swedish Medical Birth Register, we conducted a cohort study including 2,371,815 children live-born from 1987 to 2013 in Sweden, whose mother were from Nordic countries. Each child was followed from birthdate, until emigration, death, or December 31, 2016 (age ≤30 years), whichever came first. After excluding individuals with missing information on father or sex, or with conflicting information (died or emigrated prior to cohort entry), there were a total of 2,354,594 children in the final analysis.

4.2.1.2 Statistical analysis

The exposed time of ASD was defined as the birthdate of individuals with ASD because ASD is generally supposed to emerge during prenatal period[127] or very early childhood[128] and delayed diagnosis of ASD occurs commonly in clinical practice[129]. We therefore did not perform time-to-event analysis. Instead, we used Logistic regression to calculate odds ratios (ORs) and their two-sided 95% confidence intervals (CIs). To reduce potential bias due to rare events and separation[130], Firth's penalized likelihood was used. In the analysis, we first adjusted for sex and birth year (as natural cubic spline) in a simple model. Then, in a full model, we further controlled for paternal and maternal age at birth (<20, 20-29, 30-39, or ≥40 years), maternal and paternal history of psychiatric disorders (yes or no), and maternal and paternal history of cancer (yes or no). We also studied the association by type of cancer and type of ASD (i.e., autistic disorder and other ASD). To explore the impact of comorbidities, we estimated ORs among individuals with ASD alone as well as individuals with ASD with co-occurring ID, co-occurring birth defects, or both, separately. We further calculated E value[131] to estimate the influence of residual confounding on the association.

To assess constant familial confounding, we performed a sibling comparison by comparing individuals with ASD to their unaffected full siblings. We further adjusted for birth characteristics (i.e., gestational age, birth weight, Apgar score at 1 minute, and single/multiple

births), parental highest educational level, and maternal smoking during pregnancy in sensitivity analyses. We repeated the main analysis among males and females separately, to explore potential effect modification of sex.

As we did not perform a time-to-event analysis in the main analysis, we performed a separate analysis to evaluate risk of cancer following ASD diagnosis. First, we conducted a separate cohort including all individuals with ASD but without cancer at the time of ASD diagnosis. Incidence density sampling was used to randomly select 10 controls per ASD individual (individually matched by sex and birth year) from the study base, who were free of ASD and cancer at index date (i.e., date of ASD ascertainment of index case). Conditional Cox regression was used to calculate hazard ratios (HRs) and their 95% CIs of cancer. The analysis was stratified by matching identifier (sex and birth year) and adjusted for age at index date, parental age, as well as parental history of psychiatric disorders and parental history of cancer at childbirth.

To evaluate the polygenetic pleiotropy of the studied association, we used linkage disequilibrium score regression to estimate genetic correlation between ASD and cancer. GWAS summary statistics of ASD were downloaded from the Psychiatric Genomics Consortium repository, including 18,381 ASD cases and 27,969 controls (available at: http://www.med.unc.edu/pgc/results-and-downloads). The GWAS summary statistics of malignant neoplasm, including 29,617 cases with cancer and 147,282 controls, were downloaded at data freeze 4 from the FinnGen study (available at: http://r4.finngen.fi/).

4.2.2 ID and risk of cancer (Paper II)

4.2.2.1 Study design and participants

We first identified 3,557,910 live-born children born during 1974–2013 in Sweden, whose mother were from Nordic countries. We followed these children from birthdate, until emigration, death, cancer diagnosis, or end of 2016 (age ≤43 years), whichever came first. We excluded individuals lacking data on father or sex, or with contradictory information (cancer

diagnosis, emigration, or death prior to birthdate), leaving 3,531,305 children in the final analysis.

4.2.2.2 Statistical analysis

We applied Cox regression model to estimate HRs with associated 95% CIs for cancer associated with ID. We used attained age as the underlying time scale. We performed the analysis for any cancer and different cancer types. We adjusted for sex and birth year in a simple model, in which birth year was fitted as natural cubic spline. In a full model, we additionally adjusted for paternal and maternal age (<20, 20-29, 30-39, ≥40 years), maternal and paternal history of psychiatric disorders as well as maternal and paternal history of cancer at birth. We further studied the association by ID severity and ID type. We also calculated the HRs by sex, calendar period, birth characteristics, parental highest attained educational level, as well as maternal smoking during pregnancy. In addition, we performed a sibling comparison to evaluate potential familial confounding. Moreover, to examine the effect of ID on cancer among children, we repeated the main analysis among individuals with age ≤18 years. As ID might be the consequence of cancer, there is a probability of reverse causality between ID and cancer. To mitigate such concern, we conducted a sensitivity analysis where we ruled out diagnosis of CNS cancer within the first 5 years of follow-up.

4.2.3 Psychiatric disorders and cardiovascular diseases during diagnostic work-up of suspected hematological malignancy (Paper III)

4.2.3.1 Study design and participants

The study population included a total of 1,527,449 residents in Skåne, Sweden, from 2005 to 2014. Each participant was followed from January 1st, 2005, birthdate, or migration to Skåne, whichever occurred later, until ascertainment of any cancer, death, date of migration out of Skåne, or end of 2014, whichever came first. Individuals with a pre-existing cancer before start of follow-up were ruled out, leaving 1,473,204 individuals eligible for study. We divided the study participants into three groups. We first identified all patients with a newly diagnosed hematological malignancy during follow-up in the Cancer Register. We then used procedure codes in SHR to identify all individuals receiving bone marrow aspiration or biopsy or lymph

node biopsy but without receiving a diagnosis of any malignancy within six weeks after biopsy and these individuals were termed as biopsied individuals. Patients with hematological malignancy and biopsied individuals contributed their person-time during diagnostic work-up to exposed group. Reference period consisted of person-time before diagnostic work-up of patients with hematological malignancy and biopsied individuals as well as all person-time of individuals who were not classified as patients with hematological malignancy or biopsied individuals.

4.2.3.2 Definition of diagnostic work-up

We compared the number of healthcare visits each week during the twelve-week period prior to ascertainment of hematological malignancy and observed a statistically significantly number increase among patients with leukemia, myelodysplastic syndrome, as well as myeloproliferative neoplasm during the 1st week before diagnosis, compared to the week before. The increase of healthcare visits was observed at the 3rd week before cancer diagnosis for myeloma and the 5th week for lymphoma. Generally, it would take around one week from receiving cancer diagnosis to initiation of cancer treatment for aggressive hematological malignancies in Sweden[132,133]. Therefore, end of diagnostic work-up was defined as one week after diagnosis. Individuals receiving bone marrow aspiration or biopsy were defined to have the same diagnostic work-up as patients with leukemia whereas individuals receiving lymph node biopsy were defined to have the same diagnostic work-up as patients with lymphoma. Detailed definitions of diagnostic work-up for patients with hematological malignancy and biopsied individuals are listed in **Table 5**.

Table 5. Diagnostic work-up for patients with hematological malignancies and biopsied individuals

Category	Start of diagnostic work-up	End of diagnostic work-up
Patients with hematological malignancy		
Leukemia, myelodysplastic syndrome, and myeloproliferative neoplasm	1st week before diagnosis	1st week after diagnosis
Myeloma	3rd week before diagnosis	1st week after diagnosis
Lymphoma	5th week before diagnosis	1st week after diagnosis
Biopsied individuals		
Bone marrow aspiration or biopsy	1st week before diagnosis	1st week after diagnosis
Lymph node biopsy	5th week before diagnosis	1st week after diagnosis

4.2.3.3 Statistical analysis

We studied repeated outcomes of psychiatric disorders and cardiovascular disease, and all successive outcome events occurring within a 28-day period were regarded as a single event. We applied Poisson regression to estimate incidence rate ratios (IRRs) and associated 95% CIs of psychiatric disorders and cardiovascular diseases during diagnostic work-up and post-diagnostic period of a suspected hematological malignancy. All models controlled for attained age, sex, attained calendar year, civil status, history of psychiatric disorder or cardiovascular disease, and registered parish. Clustered sandwich estimators were applied to deal with intra-individual correlation due to repeated outcomes. We also performed self-comparison analysis to address invariant confounding within individuals. As patients experiencing diagnostic work-up tended to have more healthcare visits than reference group, perhaps leading to surveillance bias of studied outcomes, we performed a sensitivity analysis in which we additionally controlled for frequency of healthcare visits. Some patients with hematological malignancy might receive intensive treatment and perhaps underwent pre-therapeutic evaluation or intervention for psychiatric disorders and cardiovascular diseases during the period between diagnosis and treatment. To mitigate such concern, we compared risk of psychiatric disorders and cardiovascular diseases prior to diagnosis or biopsy to thereafter, focusing on the diagnostic work-up only.

4.2.4 Precancer psychiatric disorders and sepsis following cancer diagnosis (Paper IV)

4.2.4.1 Study design and participants

The study population included 362,500 patients aged ≥30 years, who had a new diagnosis of cancer between January 1st 2006 and December 31st 2014 in Sweden. Each patient was followed from diagnostic date of cancer, until death, migration out of Sweden, diagnostic date of sepsis, or December 31st 2014, whichever came first. We excluded cancer patients with a history of sepsis before start of follow-up as we attempted to investigate the effect of psychiatric disorders on newly onset sepsis among cancer patients. We finally included a total of 356,002 patients for analysis.

4.2.4.2 Statistical analysis

We calculated the HRs and 95% CIs for sepsis in relation to precancer psychiatric disorders using flexible parametric models. First, we plotted HRs and 95% CIs derived from flexible parametric models in which the effect of exposure can vary with time. As a persistent HR was observed over time, mean HR for the whole follow-up was presented. In all models, we used time since cohort entry as underlying time scale. We first adjusted for age at cancer diagnosis, sex, calendar period, residence region, as well as cancer type in a simple model. In a full model, we additionally controlled for marital status, highest attained educational level, cancer stage, history of infection, and Charlson Comorbidity Index score. We also separately calculated HRs for individual cancer types and different psychiatric disorders.

4.3 Ethical considerations

As Papers I-IV were all based on the Swedish national or regional population and health registers, the process of data analysis involved use of personal data. The primary aim of the thesis was to improve understanding and provide novel knowledge in the potentially bidirectional link between mental disorders and cancer, which is beneficial for prevention and early intervention of the studied disorders, improving health of patients with these disorders, and optimizing medical and social resources. When processing sensitive personal data, we need to comply with the national law and General Data Protection Regulation (PDGR). Karolinska Institutet (KI) has strict rules on access and storage of personal data to ensure data security. Data access is only limited to the researchers who are directly involved in the research and unauthorized access is prohibited. In addition, all datasets used in the thesis were pseudonymized, with separate storage of datasets and code key using approved servers under safeguard of updated antivirus and network firewall. In brief, we believe that the potential benefits of the research included in these studies outweigh the believably small harms in relation to the use of personal data.

Processing sensitive personal information is allowed for specific research purposes if it has received specific ethical approval. We have obtained ethical permissions for all four studies from the Regional Ethical Review Board in Stockholm, Sweden (reference numbers: Papers I and II: 2017/1875-31/2; Paper III: 2015/1574-31; and Paper IV: 2012/1814-31/4). Given the register-based and observational nature of the studies, informed consent from participants in these studies was exempted by the ethical approvals.

5 RESULTS

5.1 ASD and risk of cancer (Paper I)

The study included a total of 2,354,594 individuals, among whom 40,334 had a clinical diagnosis of ASD (**Table 6**). Comorbid ID and birth defects were more common among individuals with ASD than their unaffected siblings and reference group (**Table 6**). Individuals with ASD had a higher risk of developing any cancer, compared with individuals without ASD (simple model: OR 1.3, 95% CI 1.2-1.5; full model: OR 1.3, 95% CI 1.2-1.5). As results were similar between the models, all results shown below were derived through the full model. Focusing on cancer types, increased risks were also observed for cancers in eye, CNS, and thyroid gland (**Table 7**).

Table 6. Characteristics of study participants in Paper I

Characteristics	Individuals without ASD (population-control group)	Individuals with ASD	ASD-free full siblings of individuals with ASD (sibling-control group)
	N (%)	N (%)	N (%)
Number of individuals	2,278,100	40,334	36,160
Male (%)	1,164,408 (51.1%)	27,583 (68.4%)	17,859 (49.4%)
Intellectual disabilities (%)	14,011 (0.6%)	6,084 (15.1%)	598 (1.7%)
Birth defects (%)	214,568 (9.4%)	7,119 (17.7%)	3,710 (10.3%)

This table is adapted from Liu Q et al. *Annals of Oncology*, 2022[123].

Table 7. Odds ratios (ORs) and 95% confidence intervals (CIs) of cancer among individuals with ASD by cancer type, compared to population-control group

Cancer types	Full model[a]
	OR (95% CI)
Any cancer	**1.3 (1.2-1.5)**
Oral	3.0 (0.8-7.8)
Colon	1.8 (0.7-3.6)
Liver	1.4 (0.3-4.1)
Pancreas	6.2 (0.6-27.5)
Cervix	1.4 (0.3-4.1)
Ovary	1.9 (0.4-5.3)
Testis	1.4 (0.8-2.3)
Kidney	1.9 (1.0-3.3)
Bladder or other urinary organs	2.4 (0.3-8.9)
Melanoma	0.5 (0.2-1.3)
Non-melanoma skin	3.0 (0.6-8.7)
Eye	**2.5 (1.3-4.4)**
CNS	**1.8 (1.4-2.3)**
Thyroid	**2.8 (1.4-5.1)**
Other endocrine gland	1.2 (0.6-2.1)
Bone and connective tissue	0.9 (0.4-1.5)
Other or unspecified sites	2.9 (0.3-11.7)

Hodgkin’s lymphoma	1.0 (0.5-1.9)
Non-Hodgkin’s lymphoma	0.8 (0.4-1.5)
ALL	1.2 (0.8-1.7)
AML	0.9 (0.3-1.8)

[a] Full model adjusted for birth year, sex, maternal and paternal age and history of psychiatric disorder and cancer at delivery.
Bold font indicates statistically significant results.
This table is adapted from Liu Q et al. *Annals of Oncology*, 2022[123].

Individuals with autistic disorder had a higher risk increase (OR 1.7, 95% CI 1.3-2.1) than individuals with other ASD (OR 1.2, 95% CI 1.0-1.4). The positive association was mainly limited to individuals with ASD and co-occurring birth defects and ID or with ASD and co-occurring birth defects, and suggested for individuals with ASD and co-occurring ID, rather than individuals with ASD alone (**Table 8**).

The observed association remained stable by sex (OR 1.3, 95% CI 1.1-1.6 among male and OR 1.4, 95% CI 1.1-1.7 among female) and was barely changed after additional control for parental highest attained educational level, birth characteristics, or maternal smoking during pregnancy. The E-value for the overall association between ASD and cancer was calculated to be 1.9. Sibling analysis lent little support for constant familial confounding (OR 1.5, 95% CI 1.2-2.0). We also observed largely similar association (HR 1.3, 95% CI 1.03-1.7) in the matched cohort. The genetic correlation between ASD and cancer was estimated to be at -0.07 (95% CI -0.23–0.09).

Table 8. Odds ratios (ORs) and 95% confidence intervals (CIs) of any cancer among individuals with ASD, compared to the population-control group, analysis by comorbidity status with ID and birth defects

Groups	Full model[a] OR (95% CI)
Individuals with ASD	1.3 (1.2-1.5)
ASD alone	1.0 (0.8-1.2)
ASD with ID but not birth defects	1.4 (0.9-2.1)
ASD with birth defects but not ID	2.1 (1.5-2.9)
ASD with both ID and birth defects	4.8 (3.4-6.6)

[a] Full model adjusted for birth year, sex, maternal and paternal age and history of psychiatric disorder and cancer at delivery.
This table is adapted from Liu Q et al. *Annals of Oncology*, 2022[123].

5.2 ID and risk of cancer (Paper II)

The study cohort comprised 27,956 individuals with ID, and their 29,641 unaffected full siblings, as well as 3,473,708 individuals in the reference group. Individuals with ID tended to be male, compared with their unaffected siblings as well as reference group. The majority of ID cases were mild ID (54.9%, N=15,334), while the most common ID type was idiopathic ID (64.7%, N=18,078).

We observed a positive association between ID and risk of cancer (simple model: HR 1.6, 95% CI 1.4–1.8; full model: HR 1.6, 95% CI 1.4–1.8). We also observed increased risks for eleven cancer types (**Table 9**). The risk increase of any cancer was more pronounced for syndromic ID (HR 2.4, 95% CI 2.0–3.0) than idiopathic ID (HR 1.1, 95% CI 0.9–1.4).

The association was not modified greatly by sex, ID severity, calendar period, parental highest educational level, birth characteristics, or maternal smoking during pregnancy. Largely similar results were observed in the sibling analysis. The risk increase was more obvious for childhood cancer (HR 2.8, 95% CI 2.2–3.6). Excluding cases diagnosed during the five years following ID yielded similar result for CNS cancer (HR 1.6, 95% CI 1.0–2.4).

Table 9. Hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer among individuals with ID by cancer type, compared to reference group

Cancer types	Full model[a] HR (95% CI)
Any cancer	**1.6 (1.4-1.8)**
Salivary gland	1.8 (0.2-12.6)
Esophagus	**28.4 (6.2-130.6)**
Stomach	**6.1 (1.5-24.9)**
Small intestine	**12.0 (2.9-50.1)**
Colon	**2.0 (1.0-4.1)**
Rectum	2.0 (0.5-8.0)
Liver	1.4 (0.2-9.9)
Pancreas	**6.0 (1.5-24.8)**
Lung	1.1 (0.1-7.5)
Breast	0.7 (0.3-1.6)
Cervix	0.7 (0.3-1.8)
Uterus	**11.7 (1.5-90.7)**
Ovary	2.2 (0.8-5.9)
Testis	1.3 (0.8-2.1)
Kidney	**4.4 (2.0-9.8)**
Melanoma	0.8 (0.4-1.4)
Non-melanoma skin	0.9 (0.1-6.4)

Eye	1.5 (0.2-11.0)
CNS	**2.7 (2.0-3.7)**
Thyroid	1.0 (0.4-2.4)
Other endocrine gland	1.5 (0.9-2.7)
Bone	0.8 (0.2-3.3)
Connective tissue	1.5 (0.6-4.0)
Other or unspecified sites	**4.8 (1.8-12.9)**
Hodgkin's lymphoma	0.9 (0.4-1.9)
Non-Hodgkin's lymphoma	1.0 (0.4-2.3)
ALL	**2.4 (1.3-4.4)**
AML	**3.0 (1.4-6.4)**

[a] Full model adjusted for birth year, sex, maternal and paternal age and history of psychiatric disorder and cancer at delivery.
Bold font indicates statistically significant results.
This table is adapted from Liu Q et al. *PLOS Medicine*, 2021[126].

5.3 Psychiatric disorders and cardiovascular diseases during diagnostic work-up of suspected hematological malignancy (Paper III)

During follow-up, a total of 5,495 patients with hematological malignancy as well as 18,906 biopsied individuals were identified (**Table 10**). The median age of diagnosis or biopsy was 70 for patients with hematological malignancy and 56 for biopsied individuals. Most patients with hematological malignancy were male, whereas the majority of biopsied individuals were female (**Table 10**).

Table 10. Characteristics of patients with hematological malignancy and biopsied individuals in Paper III

Characteristics	Patients with hematological malignancy	Biopsied individuals
No. of patients or individuals	5,495	18,906
Male (%)	3,007 (54.7%)	8,673 (45.9%)
Median age at diagnosis or biopsy, years	70	56
Civil status		
- Cohabitating	2,917 (53.1%)	8,394 (44.4%)
- Non-cohabitating	2,578 (46.9%)	10,512 (55.6%)
History of psychiatric disorder at diagnosis or biopsy		
- Yes	961 (17.5%)	5,570 (29.5%)
- No	4,534 (82.5%)	13,336 (70.5%)
History of cardiovascular diseases at diagnosis or biopsy		
- Yes	2,749 (50.0%)	7,062 (37.4%)
- No	2,746 (50.0%)	11,844 (62.6%)

This table is adapted from Liu Q et al. *Clinical Epidemiology*, 2019[124].

5.3.1 Psychiatric disorders

Compared with reference period, we observed an increased risk of psychiatric disorders during diagnostic work-up of patients with hematological malignancy (IRR 2.1, 95% CI 1.5-2.8), which was higher than the risk increment during post-diagnostic period (IRR 1.4, 95% CI 1.1-1.7) (**Table 11**). During diagnostic work-up, the greatest risk increase was noted for stress reaction or adjustment disorder (IRR 4.4, 95% CI 2.6-7.6). We also observed a higher risk increase during diagnostic work-up (IRR 3.1, 95% CI 2.9-3.4) than post-diagnostic period (IRR 1.8, 95% CI 1.7-2.0), among biopsied individuals (**Table 11**).

Similar results were observed in the within-individual analysis and after further control for frequency of healthcare visits, for patients with hematological malignancy and biopsied individuals. Concentrating on the diagnostic work-up only, the risk increment was higher before diagnosis than thereafter, in patients with hematological malignancy and biopsied individuals (**Figure 1**).

5.3.2 Cardiovascular diseases

We observed a higher risk increase of cardiovascular diseases during diagnostic work-up (IRR 3.3, 95% CI 2.9-3.8) than post-diagnostic period (IRR 1.9, 95% CI 1.8-2.1), in patients with hematological malignancy (**Table 11**). The risk elevation was also larger during diagnostic work-up (IRR 4.9, 95% CI 4.6-5.3) than post-diagnostic period (IRR 1.9, 95% CI 1.8-2.0), in biopsied individuals (**Table 11**).

We observed similar association in the within-individual analysis and after additional control for frequency of healthcare visits. We also observed higher risk increase prior to diagnosis or biopsy compared to thereafter, when focusing on the diagnostic work-up alone (**Figure 1**).

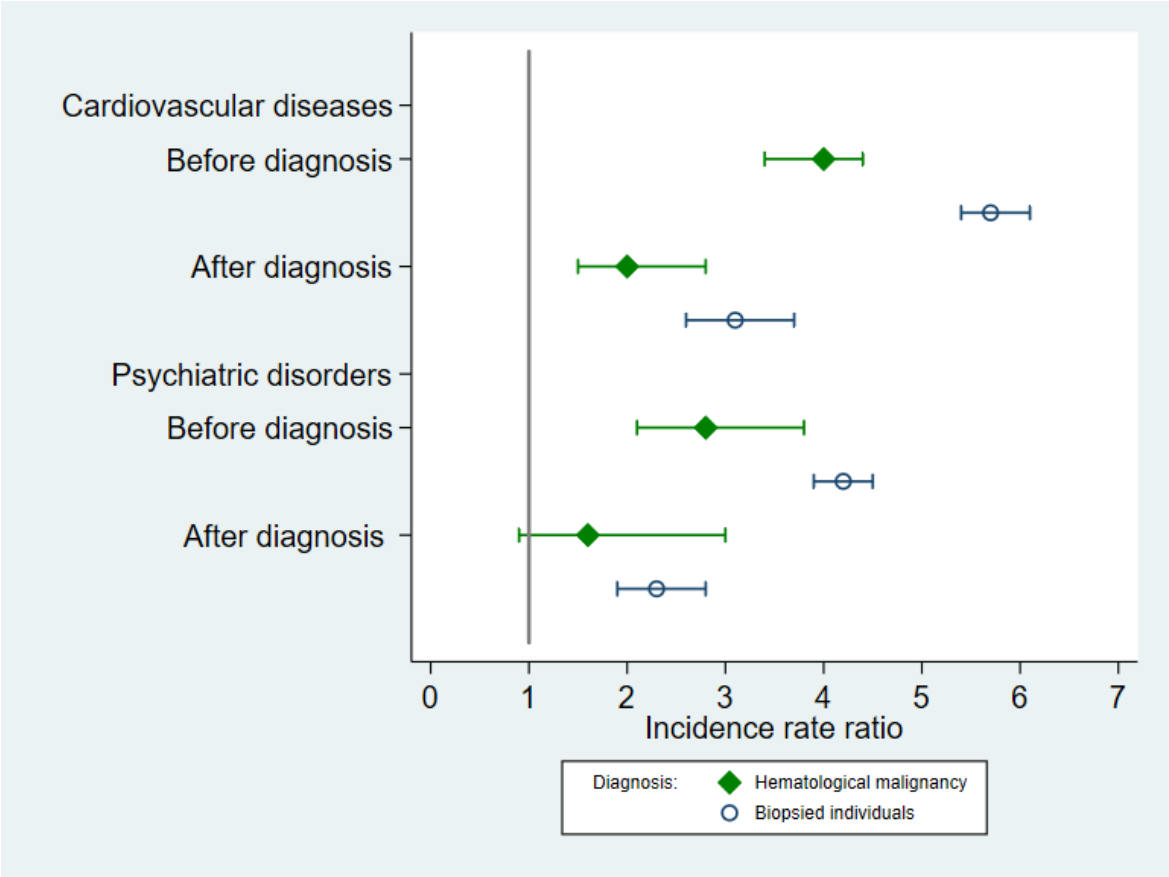
Table 11. Incidence rate ratios (IRRs) and 95% confidence intervals (CIs) of psychiatric disorders and cardiovascular diseases during the diagnostic work-up and post-diagnostic period of patients with hematological malignancy and biopsied individuals, a population-based cohort during 2005-2014 in Skåne, Sweden

	Diagnostic work-up	Post-diagnostic period
	IRR (95% CI)[a]	IRR (95% CI)[a]
Psychiatric disorders		
Reference	1.0	1.0
Patients with any hematological malignancy	2.1 (1.5-2.8)	1.4 (1.1-1.7)
Leukemia	0.5 (0.1-3.6)	1.4 (0.9-2.3)
Myelodysplastic syndrome	1.7 (0.3-11.2)	0.6 (0.2-1.8)
Myeloproliferative neoplasm	0.9 (0.1-6.4)	2.0 (1.1-3.4)
Myeloma	2.0 (0.8-5.0)	1.1 (0.6-1.9)
Lymphoma	2.3 (1.6-3.3)	1.4 (1.0-1.9)
Biopsied individuals	3.1 (2.9-3.4)	1.8 (1.7-2.0)
Individuals with bone marrow aspiration or biopsy	1.0 (0.4-2.1)	1.4 (1.1-1.9)
Individuals with lymph node biopsy	3.2 (2.9-3.5)	1.9 (1.8-2.0)
Cardiovascular disease		
Reference[b]	1.0	1.0
Patients with any hematological malignancy	3.3 (2.9-3.8)	1.9 (1.8-2.1)
Leukemia	6.4 (4.4-9.1)	2.6 (2.1-3.3)
Myelodysplastic syndrome	3.3 (1.7-6.4)	1.7 (1.2-2.3)
Myeloproliferative neoplasm	5.4 (3.6-8.1)	2.0 (1.5-2.6)

Myeloma	3.3 (2.3-4.7)	1.7 (1.4-2.1)
Lymphoma	3.0 (2.6-3.5)	1.9 (1.7-2.1)
Biopsied individuals	4.9 (4.6-5.3)	1.9 (1.8-2.0)
Individuals with bone marrow aspiration or biopsy	7.0 (5.8-8.5)	2.5 (2.2-2.8)
Individuals with lymph node biopsy	4.8 (4.5-5.1)	1.8 (1.7-1.9)

[a] Adjusted for attained age and calendar year, sex, civil status, preexisting cardiovascular disease or psychiatric disorder, and registered parish.
This table is adapted from Liu Q et al. *Clinical Epidemiology*, 2019[124].

Figure 1. Incidence rate ratios (IRRs) and their 95% confidence intervals (CIs) of cardiovascular diseases and psychiatric disorders during the diagnostic work-up of patients with hematological malignancy or biopsied individuals, separating the analyses by before or after date of diagnosis or biopsy



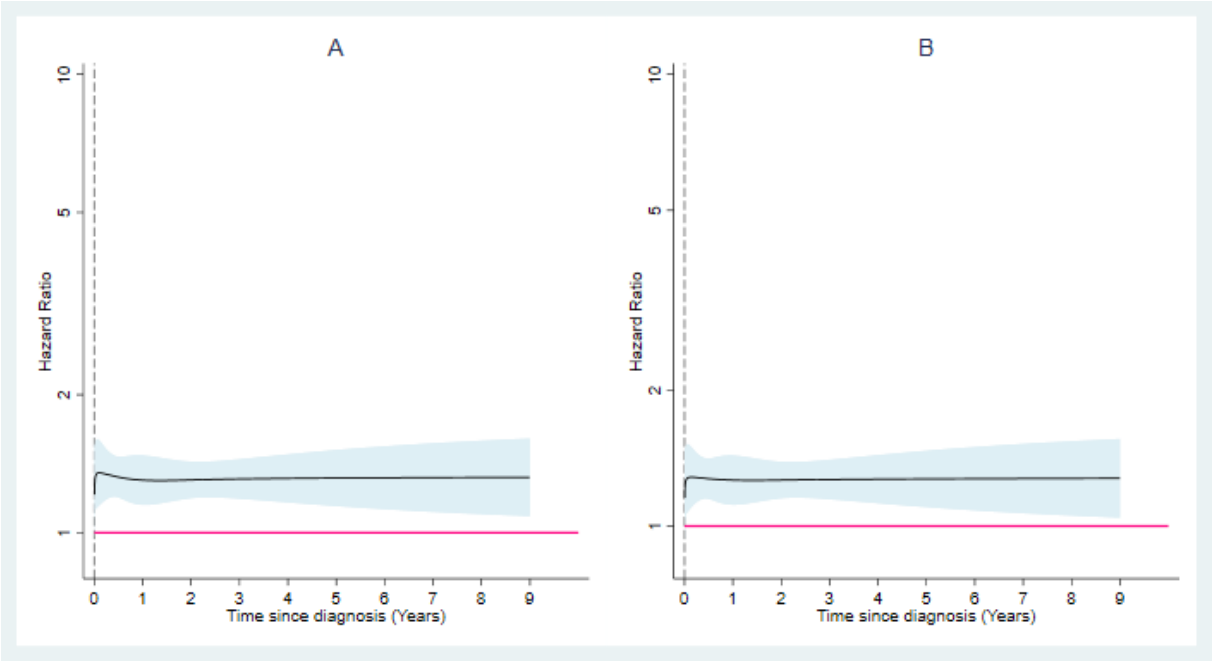
This figure is taken from Liu Q et al. *Clinical Epidemiology*, 2019[124].

5.4 Precancer psychiatric disorders and sepsis following cancer diagnosis (Paper IV)

The study included 22,609 cancer patients with precancer psychiatric disorders and 333,393 cancer patients free of such comorbidity. The median age of cancer diagnosis was 64 and 68 for exposed and reference group, respectively. We observed an association between precancer psychiatric disorders and risk of sepsis following cancer diagnosis (**Figure 2**). Given the persistent risk increase during the whole follow-up, HRs shown below were obtained in models that hold proportional hazard assumption of the effect of exposure. We observed similar risk increase between the simple model (HR, 1.3; 95% CI, 1.2–1.4) and full model (HR, 1.3; 95% CI, 1.2–1.4).

Similar associations were observed for most studied cancer types, with the highest risk increase noted for breast cancer and prostate cancer as well as other types of cancer (**Table 12**). We also found similar risk increase for the majority of studied psychiatric disorders, with the greatest risk increase observed for substance abuse (**Table 12**).

Figure 2. Hazard ratio and 95% confidence interval of sepsis among cancer patients with precancer psychiatric disorders compared to cancer patients without precancer psychiatric disorders



Hazard ratios were estimated through flexible parametric survival models, allowing the effect of psychiatric disorders and cancer type to vary over time. (A) adjusted for sex, age, calendar period, residence region, and cancer type (simple model). (B) further adjusted for marital status, educational level, cancer stage, infection history and Charlson Comorbidity Index score (full model).
This figure is adapted from Liu Q et al. *Cancer Research*, 2020[125].

Table 12. Hazard ratios (HR) and 95% confidence intervals (CIs) of sepsis among cancer patients with precancer psychiatric disorders compared to cancer patients without precancer psychiatric disorders, analysis by types of cancer and psychiatric disorders

Characteristics	Full model[a] HR (95% CI)
By cancer type	
Any	1.3 (1.2-1.4)
Prostate	1.3 (1.1-1.6)
Breast	1.4 (1.1-1.7)
Colorectal	1.2 (1.0-1.5)
Lung	1.2 (0.9-1.5)
Non-melanoma skin	0.9 (0.6-1.5)
CNS	1.1 (0.6-1.9)
Hematological	1.0 (0.8-1.2)
Other	1.4 (1.3-1.6)
By type of psychiatric disorder	
Depression	1.3 (1.1-1.5)
Anxiety	1.2 (1.0-1.5)
Stress reaction and adjustment disorder	1.0 (0.8-1.3)
Substance abuse	1.4 (1.2-1.6)
Somatoform/conversion disorder	1.1 (0.8-1.5)
Other	1.3 (1.1-1.5)

[a] In the analyses by cancer type, full model adjusted for sex, age, calendar period, residence region, marital status, educational level, cancer stage, infection history and Charlson Comorbidity Index score; In the analyses by type of psychiatric disorders, full model adjusted for sex, age, calendar period, residence region, cancer type, marital status, educational level, cancer stage, infection history and Charlson Comorbidity Index score, and the effect of cancer type was allowed to vary over time.
This table is adapted from Liu Q et al. *Cancer Research*, 2020[125]

6 DISCUSSION

6.1 General discussion

6.1.1 ASD, ID and risk of cancer

We investigated the association between ASD, ID and risk of cancer and observed elevated risk of cancer among individuals with general ASD and ID in Papers I and II, respectively. For ASD, we further revealed that the risk increase of cancer was predominantly limited to those with comorbid ID and/or birth defects, instead of ASD alone. For ID, we also demonstrated that increased risk of cancer was more pronounced for syndromic ID, rather than idiopathic ID.

One possible explanation of the observed findings would be that congenital malformations or syndromes might impact multiple systems or organs[134-136]. ASD, ID, or ASD with comorbid ID could be regarded as manifestations of various congenital malformations or syndromes, which might also impact other systems and contribute to the pathogenesis of cancer. Markedly increased risk of any cancer noted in ASD with co-occurring ID and/or birth defects, as well as syndromic ID, suggests that genetic or chromosomal abnormalities might contribute to the observed findings. Similar associations observed in sibling analysis, together with scant effect of polygenetic pleiotropy between ASD and cancer in the genetic correlation analysis, further indicates a potential role of rare genetic mutations, *de novo* genetic variants, copy number variations, or chromosomal abnormalities in the observed associations. In addition, differences of lifestyle factors between individuals with ASD or ID and general population, such as obesity[137,138], physical inactivity[138,139], and poor diet[140,141], might also contribute to the observed associations.

6.1.2 Psychiatric disorders and cardiovascular diseases during diagnostic work-up of hematological malignancy

In Paper III, we found higher-than-expected risks of both psychiatric disorders and cardiovascular diseases during diagnostic work-up of a suspected hematological malignancy. During diagnostic work-up, the risk increase was larger while waiting for diagnosis (from

start of diagnostic work-up until diagnosis) than while waiting for treatment (from diagnosis until treatment).

Psychological distress due to invasive examination, uncertainty of final diagnosis, and decision making on treatment (if receiving a diagnosis of hematological malignancy) could directly lead to psychiatric disorders. Such psychological distress could also induce cardiovascular disease. In addition to stress, the underlying malignant disease might also play a role in the observed associations, especially for cardiovascular disease. For instance, some patients with suspected hematological malignancy might experience anemia or bleeding, which could directly contribute to the pathogenesis of cardiovascular disease[142]. Moreover, adaptive changes in response to psychological distress, including changed levels of inflammatory or metabolic biomarkers, might also involve in the development of psychiatric disorders as well as cardiovascular disease[45,48-51,143,144].

6.1.3 Precancer psychiatric disorders and sepsis following cancer diagnosis

In Paper IV, we observed an association between precancer psychiatric disorders and an increased risk of sepsis following cancer diagnosis. The risk elevated directly after cancer diagnosis and lasted until the end of follow-up (nine years). Our findings extended previous knowledge of an association between psychiatric disorders and sepsis in general population[145], by demonstrating such an association among cancer patients.

Psychiatric disorders could induce immune dysfunction through the effect of psychological distress on sympathetic nervous system as well as HPA axis[5,146]. Accumulating evidence has demonstrated that psychological distress could alter immune process through a series of changes in immune responses, including reduced antibody production, inhabitation of T-cell function, and altered levels of inflammatory cytokines[45,48-51,147], which might further lead to initiation and progression of infection. Disparities in health care between patients with psychiatric disorders and those without such comorbidity might also play a role in the association. For example, patients with psychiatric disorders tend to have less healthcare visits as well as experience non-compliance in treatment[148,149], which could lead to delayed diagnosis of cancer and infection, and thus promote the development of sepsis. Besides,

behavioral habits among patients with psychiatric disorders such as smoking and alcohol use might also play a role.

6.2 Methodological considerations

6.2.1 Selection bias

Selection bias is a common bias in observational studies and occurs when the studied parameters in sub-population available for analysis deviated from that in target population[150]. All studies in the thesis are based on population and health registers that cover all residents in Sweden or Skåne. In Papers I and II, we used information on all live-born children identified from the Swedish Medical Birth Register, which has a coverage of nearly 100%. In Paper III, we used information on the entire population residing in the region of Skåne. In Paper IV, study participants were obtained from the Swedish Cancer Register which is also nationwide since 1958. As a result, the high coverage of these registers largely minimized potential selection bias.

6.2.2 Information bias

Misclassification is one concern of the thesis, as all information on exposures and outcomes was collected from the Swedish population and health registers. It may have introduced some bias in the study results. For instance, in Papers I, II, and IV, as mental disorders (ASD, ID or psychiatric disorders) were identified through the Swedish Patient Register, which includes information only on hospital-based specialist care, they represented relatively severe conditions. As a result, mild cases and asymptomatic cases were not identified. Similarly, identification of outcomes might also suffer from misclassification (i.e., Paper III). However, the outcome ascertainment in Papers I and II (i.e., cancer) and Paper IV (i.e., sepsis) is likely both sensitive and specific due to the high quality of cancer registration and the severeness of sepsis. Regardless, as information on exposures and outcomes is collected independently of each other, such misclassification might have most likely diluted the observed associations and impacted the estimates towards null.

Individuals with one disease might experience more intensive survey and are more likely to be detected or diagnosed with another disease. Such surveillance bias might also distort the association of interest. In the thesis, on the one hand, patients with an exposure disease (e.g., mental disorder) might tend to have more frequent healthcare visits and greater likelihood of ascertainment for the diagnosis of outcome (e.g., cancer). On the other hand, however, patients with mental disorders (Papers I, II and IV) might also be less likely to report their symptoms or signs and have less healthcare visits[148,149,151], perhaps leading to underdiagnosis or delayed diagnosis of outcomes. Of note, in Paper III, as the exposure was diagnostic work-up of suspected hematological malignancy, surveillance bias might be larger in this study, compared to other studies. However, similar association was observed after adjusting for frequency of healthcare visits in Paper III and alleviated such concern to some extent.

6.2.3 Confounding

Theoretically, any association of observational studies might be distorted by potential confounders. Such applies to all studies of the thesis as well. To alleviate the concern of confounding, we adjusted for various confounders in the analysis of each study. In Papers I and II, we additionally performed sibling comparison to address constant familial confounding. In Paper III, we further performed self-comparison analysis to address confounding that are persistent over time.

Although we tried to control for a series of confounders, we had limited data on some other confounders. For instance, in Papers I and II, we had no information on environmental factors, which might impact the formation of brain in prenatal life and early childhood as well as risk of cancer. In Papers III and IV, we had limited information on lifestyle factors and treatment of cancer. Moreover, residual confounding might not be fully addressed by the methods used in our studies. For instance, sibling comparison could not address the issue of non-constant familial confounding. Similarly, self-comparison could not control for time-varying confounding within individuals.

To estimate the influence of unmeasured confounders, we calculated E-value in Paper I and found that any unmeasured confounder needed to have a minimal relative risk of 1.9 for both

ASD and cancer to totally distort the studied association. Although we did not calculate E-value in other studies, the E-value of the main findings in other studies must be more than or close to that in Paper I, as the relative risks in those studies were no less than that in Paper I.

6.2.4 External validity

External validity (generalizability) refers to the degree of findings in one study that can be applied to the whole population or under other settings. Given the high coverage of the registers used in the thesis, the generalizability of findings to the whole Swedish population is good. However, as the Swedish Cancer Register and Patient Register were based on hospital settings, mild psychiatric disorders or indolent cancers with no obvious symptoms or signs might not have been recorded in these registers. Generalizability of the findings to these cases should be cautious. Besides, generalizability of the findings to other countries that do not have universal healthcare as that in Sweden also needs further assessment.

7 CONCLUSIONS

ASD, when co-occurring with ID/birth defects, was related to cancer risk in early life, whereas ASD without such comorbidities had similar risk of cancer as general population. Our finding identified a high-risk group among individuals with ASD for potential surveillance and intervention of cancer, and provides clues for further research about mechanisms linking ASD and cancer.

ID was related to an increased risk of any cancer and eleven cancer types, up to age 43. The risk increase of any cancer was more pronounced for syndromic ID. Our results call for extended surveillance and intervention of cancer in patients with ID.

Evaluation for a suspected hematological malignancy was associated with increased risks of cardiovascular diseases and psychiatric disorders. The risk increases were greater while waiting for the final diagnosis than thereafter.

Precancer psychiatric disorders were related to increased risk of subsequent sepsis following cancer diagnosis. Our findings extend previous knowledge of the association between psychiatric disorders and sepsis among general population to cancer patients.

8 POINTS OF PERSPECTIVE

Although there is exciting progress in our understanding of the role of mental disorders on cancer, important knowledge gaps remain. Multinational population-based studies with long follow-up as well as detailed information on environmental factors are needed to better demonstrate the association between neurodevelopmental disorders and cancer, especially for rare cancer types and late-onset cancers. In addition, more research is needed in exploring the temporal pattern of the risk of mental disorders during entire disease process of cancer, starting from before diagnosis (including diagnostic work-up), to diagnosis, primary treatment, salvage treatment, disease relapse, onset of secondary cancer or severe comorbidities, until the end-of-life care. More attention is also needed on the impact of mental disorders on somatic comorbidities of cancer.

It is a crucial and challenging issue to differentiate mental disorders according to their underlying mechanisms. Different from cancer, most mental disorders are diagnosed based on symptoms. Diagnoses based on symptoms are generally limited[152], even though the diagnostic criteria have been updated over time. Symptom-based diagnoses might therefore lead to ignoration of the underlying heterogeneity of mental disorders, which is key to the identification of both vulnerable populations and targeted treatment. For instance, depression that is greatly attributable to psychological distress and depression that is more attributable to chronic inflammation may demonstrate largely similar symptoms, with however different underlying biology and response to treatment. Given the immune dysfunction of cancer, inflammatory cytokine panels are promising tools to understand the link between cancer and mental disorders[71,153]. As a result, combination of traditional psychiatric medications with anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and cytokine-inhibitors, might yield favorable effect in the treatment of cancer patients with comorbid mental disorders[154].

For patients with cancer, symptoms of some mental disorders might serve as a reflection of abnormal levels of inflammatory cytokines or endocrine changes, which could be used as early indicators of changes of disease status. For instance, mental disorders might be potential indicators of early relapse, secondary cancer occurrence, or onset of severe complications (e.g., sepsis, cardiovascular disease, or diabetes). Such hypotheses need to be tested in future research.

9 ACKNOWLEDGEMENTS

Fang Fang, my main supervisor, thank you for introducing me to the interesting world of Epidemiology. Thank you for your "sister-like" patience, support, and care, not only in my research work but also in my personal life. Thank you for your unconditional trust and endless encouragement during my whole PhD study. I really enjoy my PhD period so that I am a bit unwilling to depart from the unforgettable time under your supervision.

Karin Ekström Smedby, my co-supervisor, thank you for sharing your broad and profound knowledge in Hematology, Oncology, and Clinical Epidemiology. Thank you for your kindness and patience when guiding me and in my research projects. **Therese Andersson**, my co-supervisor, thank you for teaching me Biostatistics. Thank you for your wise suggestions and comments as well as insightful discussions to all the studies. **Patrik Magnusson**, my co-supervisor, thank you for always encouraging me and talking with me to help me practice English speaking. You are very kind and easy to talk and work with. **Sven Sandin**, thank you for the opportunity to work with you on the projects of ID and ASD. Thank you for your patient guidance in statistical codes, writing, and formats of submission. Xie Xie.

Special thanks to **Xu Chen** for introducing me to KI and MEB.

Thanks also to my family, friends, all members in the Unit of Integrative Epidemiology, colleagues at IMM and MEB, all co-authors, collaborators, as well as those who would look for their names in the Acknowledgement part but would fail--I do not put your names in a long list, but in mind and heart.

10 REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA: a cancer journal for clinicians 2022;72:7-33.
2. Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet (London, England) 2013;382:1575-86.
3. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol 2011;12:160-74.
4. Mehnert A, Brahler E, Faller H, et al. Four-week prevalence of mental disorders in patients with cancer across major tumor entities. J Clin Oncol 2014;32:3540-6.
5. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nature reviews Immunology 2005;5:243-51.
6. Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. The Lancet Oncology 2004;5:617-25.
7. Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. Brain, behavior, and immunity 2013;30 Suppl:S41-7.
8. Jia Y, Li F, Liu YF, Zhao JP, Leng MM, Chen L. Depression and cancer risk: a systematic review and meta-analysis. Public health 2017;149:138-48.
9. Gross AL, Gallo JJ, Eaton WW. Depression and cancer risk: 24 years of follow-up of the Baltimore Epidemiologic Catchment Area sample. Cancer causes & control : CCC 2010;21:191-9.
10. Chen YH, Lin HC. Increased risk of cancer subsequent to severe depression--a nationwide population-based study. Journal of affective disorders 2011;131:200-6.
11. O'Neill S, Posada-Villa J, Medina-Mora ME, et al. Associations between DSM-IV mental disorders and subsequent self-reported diagnosis of cancer. Journal of psychosomatic research 2014;76:207-12.
12. Goldacre MJ, Wotton CJ, Yeates D, Seagroatt V, Flint J. Cancer in people with depression or anxiety: record-linkage study. Social psychiatry and psychiatric epidemiology 2007;42:683-9.
13. Archer G, Pikhart H, Head J. Do depressive symptoms predict cancer incidence?: 17-year follow-up of the Whitehall II study. Journal of psychosomatic research 2015;79:595-603.
14. Lemogne C, Consoli SM, Melchior M, et al. Depression and the risk of cancer: a 15-year follow-up study of the GAZEL cohort. American journal of epidemiology 2013;178:1712-20.
15. Wang D, Cheng Z, Zhao X, et al. Association between MKL1 rs6001946 and schizophrenia in a Han Chinese population. Neuroscience letters 2016;631:36-9.
16. D'Souza H, Karmiloff-Smith A. Neurodevelopmental disorders. Wiley interdisciplinary reviews Cognitive science 2017;8.
17. Thapar A, Cooper M, Rutter M. Neurodevelopmental disorders. The Lancet Psychiatry 2017;4:339-46.
18. Saida S. Predispositions to Leukemia in Down Syndrome and Other Hereditary Disorders. Current treatment options in oncology 2017;18:41.
19. Mateos MK, Barbaric D, Byatt SA, Sutton R, Marshall GM. Down syndrome and leukemia: insights into leukemogenesis and translational targets. Translational pediatrics 2015;4:76-92.
20. Zhukova N, Naqvi A. Williams-Beuren Syndrome and Burkitt Leukemia. Journal of pediatric hematology/oncology 2013;35:e30-2.

21. Amenta S, Moschovi M, Sofocleous C, Kostaridou S, Mavrou A, Fryssira H. Non-Hodgkin lymphoma in a child with Williams syndrome. Cancer genetics and cytogenetics 2004;154:86-8.
22. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet (London, England) 2000;355:165-9.
23. Boker LK, Merrick J. Cancer incidence in persons with Down syndrome in Israel. Down's syndrome, research and practice : the journal of the Sarah Duffen Centre 2002;8:31-6.
24. Sullivan SG, Hussain R, Threlfall T, Bittles AH. The incidence of cancer in people with intellectual disabilities. Cancer causes & control : CCC 2004;15:1021-5.
25. Lauritsen MB, Mors O, Mortensen PB, Ewald H. Medical disorders among inpatients with autism in Denmark according to ICD-8: a nationwide register-based study. Journal of autism and developmental disorders 2002;32:115-9.
26. Linendoll N, Saunders T, Burns R, et al. Health-related quality of life in Hodgkin lymphoma: a systematic review. Health and quality of life outcomes 2016;14:114.
27. Mols F, Aaronson NK, Vingerhoets AJ, et al. Quality of life among long-term non-Hodgkin lymphoma survivors: a population-based study. Cancer 2007;109:1659-67.
28. Abuelgasim KA, Ahmed GY, Alqahtani JA, Alayed AM, Alaskar AS, Malik MA. Depression and anxiety in patients with hematological malignancies, prevalence, and associated factors. Saudi medical journal 2016;37:877-81.
29. Baytan B, Asut C, Cirpan Kantarcioglu A, Sezgin Evim M, Gunes AM. Health-Related Quality of Life, Depression, Anxiety, and Self-Image in Acute Lymphocytic Leukemia Survivors. Turkish journal of haematology : official journal of Turkish Society of Haematology 2016;33:326-30.
30. Kunin-Batson AS, Lu X, Balsamo L, et al. Prevalence and predictors of anxiety and depression after completion of chemotherapy for childhood acute lymphoblastic leukemia: A prospective longitudinal study. Cancer 2016;122:1608-17.
31. Zebrack BJ, Zeltzer LK, Whitton J, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study. Pediatrics 2002;110:42-52.
32. Lu D, Andersson TM, Fall K, et al. Clinical Diagnosis of Mental Disorders Immediately Before and After Cancer Diagnosis: A Nationwide Matched Cohort Study in Sweden. JAMA oncology 2016;2:1188-96.
33. Mohammadi M, Cao Y, Glimelius I, Bottai M, Eloranta S, Smedby KE. The impact of comorbid disease history on all-cause and cancer-specific mortality in myeloid leukemia and myeloma - a Swedish population-based study. BMC cancer 2015;15:850.
34. Awsare NS, Green JS, Aldwinckle B, Hanbury DC, Boustead GB, McNicholas TA. The measurement of psychological distress in men being investigated for the presence of prostate cancer. Prostate cancer and prostatic diseases 2008;11:384-9.
35. Cordova MJ, Riba MB, Spiegel D. Post-traumatic stress disorder and cancer. The lancet Psychiatry 2017;4:330-8.
36. Medeiros M, Oshima CT, Forones NM. Depression and anxiety in colorectal cancer patients. Journal of gastrointestinal cancer 2010;41:179-84.
37. Frick E, Tyroller M, Panzer M. Anxiety, depression and quality of life of cancer patients undergoing radiation therapy: a cross-sectional study in a community hospital outpatient centre. European journal of cancer care 2007;16:130-6.
38. Greenberg DB, Kornblith AB, Herndon JE, et al. Quality of life for adult leukemia survivors treated on clinical trials of Cancer and Leukemia Group B during the period 1971-1988: predictors for later psychologic distress. Cancer 1997;80:1936-44.
39. Smith SK, Williams CS, Zimmer CR, Zimmerman S. An exploratory model of the relationships between cancer-related trauma outcomes on quality of life in non-Hodgkin lymphoma survivors. Journal of psychosocial oncology 2011;29:19-34.

40. Mosher CE, Redd WH, Rini CM, Burkhalter JE, DuHamel KN. Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature. Psycho-oncology 2009;18:113-27.
41. Unseld M, Krammer K, Lubowitzki S, et al. Screening for post-traumatic stress disorders in 1017 cancer patients and correlation with anxiety, depression, and distress. Psycho-oncology 2019;28:2382-8.
42. Warchala A, Krupka-Matuszczyk I, Krysta K. Anxiety and depression in patients with acute leukaemia treated with hematopoietic stem cell transplantation. Psychiatria Danubina 2019;31:231-6.
43. Taylor S, Asmundson GJ, Carleton RN, Brundin P. Acute posttraumatic stress symptoms and depression after exposure to the 2005 Saskatchewan Centennial Air Show disaster: prevalence and predictors. American journal of disaster medicine 2007;2:217-30.
44. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. The lancet Psychiatry 2015;2:258-70.
45. Kivimäki M, Shipley MJ, Batty GD, et al. Long-term inflammation increases risk of common mental disorder: a cohort study. Molecular psychiatry 2014;19:149-50.
46. Raison CL, Miller AH. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). Molecular psychiatry 2013;18:15-37.
47. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nature reviews Neuroscience 2008;9:46-56.
48. Mørch RH, Dieset I, Faerden A, et al. Persistent increase in TNF and IL-1 markers in severe mental disorders suggests trait-related inflammation: a one year follow-up study. Acta psychiatrica Scandinavica 2017;136:400-8.
49. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biological psychiatry 2008;63:801-8.
50. Upthegrove R, Manzanares-Teson N, Barnes NM. Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. Schizophrenia research 2014;155:101-8.
51. Quagliato LA, Nardi AE. Cytokine alterations in panic disorder: A systematic review. Journal of affective disorders 2017;228:91-6.
52. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biological psychiatry 2011;70:663-71.
53. Kirkpatrick B, Miller BJ. Inflammation and schizophrenia. Schizophrenia bulletin 2013;39:1174-9.
54. Morch RH, Dieset I, Faerden A, et al. Persistent increase in TNF and IL-1 markers in severe mental disorders suggests trait-related inflammation: a one year follow-up study. Acta psychiatrica Scandinavica 2017;136:400-8.
55. Liu Y, Al-Sayegh H, Jabrah R, Wang W, Yan F, Zhang J. Association between C-reactive protein and depression: modulated by gender and mediated by body weight. Psychiatry research 2014;219:103-8.
56. Wium-Andersen MK, Orsted DD, Nielsen SF, Nordestgaard BG. Elevated C-reactive protein levels, psychological distress, and depression in 73, 131 individuals. JAMA psychiatry 2013;70:176-84.
57. Wium-Andersen MK, Orsted DD, Nordestgaard BG. Elevated C-reactive protein and late-onset bipolar disorder in 78 809 individuals from the general population. The British journal of psychiatry : the journal of mental science 2016;208:138-45.

58. Dickerson F, Stallings C, Origoni A, Boronow J, Yolken R. Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. Progress in neuro-psychopharmacology & biological psychiatry 2007;31:952-5.
59. De Berardis D, Conti CM, Campanella D, et al. Evaluation of C-reactive protein and total serum cholesterol in adult patients with bipolar disorder. International journal of immunopathology and pharmacology 2008;21:319-24.
60. Inoshita M, Numata S, Tajima A, et al. A significant causal association between C-reactive protein levels and schizophrenia. Scientific reports 2016;6:26105.
61. Fawzi MH, Fawzi MM, Fawzi MM, Said NS. C-reactive protein serum level in drug-free male Egyptian patients with schizophrenia. Psychiatry research 2011;190:91-7.
62. Akanji AO, Ohaeri JU, Al-Shammri S, Fatania HR. Association of blood levels of C-reactive protein with clinical phenotypes in Arab schizophrenic patients. Psychiatry research 2009;169:56-61.
63. Morrison VA. Infections in patients with leukemia and lymphoma. Cancer treatment and research 2014;161:319-49.
64. Zembower TR. Epidemiology of infections in cancer patients. Cancer treatment and research 2014;161:43-89.
65. Motivala SJ, Sarfatti A, Olmos L, Irwin MR. Inflammatory markers and sleep disturbance in major depression. Psychosomatic medicine 2005;67:187-94.
66. Malhi GS, Mann JJ. Depression. Lancet (London, England) 2018;392:2299-312.
67. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. Nature reviews Clinical oncology 2014;11:597-609.
68. Büttner-Teleagă A, Kim YT, Osel T, Richter K. Sleep Disorders in Cancer-A Systematic Review. International journal of environmental research and public health 2021;18.
69. Jatoi A. Weight loss in patients with advanced cancer: effects, causes, and potential management. Current opinion in supportive and palliative care 2008;2:45-8.
70. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biological psychiatry 2009;65:732-41.
71. Young K, Singh G. Biological Mechanisms of Cancer-Induced Depression. Frontiers in psychiatry 2018;9:299.
72. Segal DS, Kuczenski R, Mandell AJ. Theoretical implications of drug-induced adaptive regulation for a biogenic amine hypothesis of affective disorder. Biological psychiatry 1974;9:147-59.
73. Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues in clinical neuroscience 2006;8:383-95.
74. Egeland M, Zunszain PA, Pariante CM. Molecular mechanisms in the regulation of adult neurogenesis during stress. Nature reviews Neuroscience 2015;16:189-200.
75. Schmidt ME, Goldschmidt S, Hermann S, Steindorf K. Late effects, long-term problems and unmet needs of cancer survivors. International journal of cancer 2022.
76. Hellstadius Y, Lagergren J, Zylstra J, et al. A longitudinal assessment of psychological distress after oesophageal cancer surgery. Acta oncologica (Stockholm, Sweden) 2017;56:746-52.
77. von der Weid NX. Adult life after surviving lymphoma in childhood. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 2008;16:339-45.
78. Yiannopoulou KG, Anastasiou AI, Kontoangelos K, Papageorgiou C, Anastasiou IP. Cognitive and Psychological Impacts of Different Treatment Options for Prostate Cancer: A Critical Analysis. Current urology 2020;14:169-77.

79. Kim JH, Brown SL, Jenrow KA, Ryu S. Mechanisms of radiation-induced brain toxicity and implications for future clinical trials. Journal of neuro-oncology 2008;87:279-86.
80. Baker WJ, Royer GL, Jr., Weiss RB. Cytarabine and neurologic toxicity. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1991;9:679-93.
81. Fardet L, Petersen I, Nazareth I. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. The American journal of psychiatry 2012;169:491-7.
82. Arana GW, Santos AB, Laraia MT, et al. Dexamethasone for the treatment of depression: a randomized, placebo-controlled, double-blind trial. The American journal of psychiatry 1995;152:265-7.
83. DeBattista C, Posener JA, Kalehzan BM, Schatzberg AF. Acute antidepressant effects of intravenous hydrocortisone and CRH in depressed patients: a double-blind, placebo-controlled study. The American journal of psychiatry 2000;157:1334-7.
84. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436-44.
85. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis 2009;30:1073-81.
86. Cozen W, Gill PS, Ingles SA, et al. IL-6 levels and genotype are associated with risk of young adult Hodgkin lymphoma. Blood 2004;103:3216-21.
87. Stoll JR, Vaidya TS, Mori S, Dusza SW, Lacouture ME, Markova A. Association of interleukin-6 and tumor necrosis factor-α with mortality in hospitalized patients with cancer. Journal of the American Academy of Dermatology 2021;84:273-82.
88. Jourdan M, Tarte K, Legouffe E, Brochier J, Rossi JF, Klein B. Tumor necrosis factor is a survival and proliferation factor for human myeloma cells. European cytokine network 1999;10:65-70.
89. Sharpe CR, Collet JP, Belzile E, Hanley JA, Boivin JF. The effects of tricyclic antidepressants on breast cancer risk. British journal of cancer 2002;86:92-7.
90. Serafeim A, Grafton G, Chamba A, et al. 5-Hydroxytryptamine drives apoptosis in biopsylike Burkitt lymphoma cells: reversal by selective serotonin reuptake inhibitors. Blood 2002;99:2545-53.
91. Xia D, Zhang YT, Xu GP, Yan WW, Pan XR, Tong JH. Sertraline exerts its antitumor functions through both apoptosis and autophagy pathways in acute myeloid leukemia cells. Leukemia & lymphoma 2017;58:1-10.
92. Baú-Carneiro JL, Akemi Guirao Sumida I, Gallon M, Zaleski T, Boia-Ferreira M, Bridi Cavassin F. Sertraline repositioning: an overview of its potential use as a chemotherapeutic agent after four decades of tumor reversal studies. Translational oncology 2022;16:101303.
93. Walker AJ, Card T, Bates TE, Muir K. Tricyclic antidepressants and the incidence of certain cancers: a study using the GPRD. British journal of cancer 2011;104:193-7.
94. Dalton SO, Johansen C, Mellemkjaer L, et al. Antidepressant medications and risk for cancer. Epidemiology (Cambridge, Mass) 2000;11:171-6.
95. Bahl S, Cotterchio M, Kreiger N, Klar N. Antidepressant medication use and non-Hodgkin's lymphoma risk: no association. American journal of epidemiology 2004;160:566-75.
96. Lowry SJ, Chubak J, Press OW, McKnight B, Weiss NS. Risk of non-Hodgkin lymphoma in relation to tricyclic antidepressant use. Annals of epidemiology 2013;23:349-54.

97. Wernli KJ, Hampton JM, Trentham-Dietz A, Newcomb PA. Antidepressant medication use and breast cancer risk. Pharmacoepidemiology and drug safety 2009;18:284-90.
98. Cosgrove L, Shi L, Creasey DE, Anaya-McKivergan M, Myers JA, Huybrechts KF. Antidepressants and breast and ovarian cancer risk: a review of the literature and researchers' financial associations with industry. PloS one 2011;6:e18210.
99. Xu W, Tamim H, Shapiro S, Stang MR, Collet JP. Use of antidepressants and risk of colorectal cancer: a nested case-control study. The Lancet Oncology 2006;7:301-8.
100. Tamim HM, Mahmud S, Hanley JA, Boivin JF, Stang MR, Collet JP. Antidepressants and risk of prostate cancer: a nested case-control study. Prostate cancer and prostatic diseases 2008;11:53-60.
101. González-Pérez A, García Rodríguez LA. Breast cancer risk among users of antidepressant medications. Epidemiology (Cambridge, Mass) 2005;16:101-5.
102. Lu D, Song J, Lu Y, et al. A shared genetic contribution to breast cancer and schizophrenia. Nature communications 2020;11:4637.
103. Zhu GL, Xu C, Yang KB, et al. Causal relationship between genetically predicted depression and cancer risk: a two-sample bi-directional mendelian randomization. BMC cancer 2022;22:353.
104. Qi H, Dong C, Chung WK, Wang K, Shen Y. Deep Genetic Connection Between Cancer and Developmental Disorders. Human mutation 2016;37:1042-50.
105. Shen W, Heeley JM, Carlston CM, et al. The spectrum of DNMT3A variants in Tatton-Brown-Rahman syndrome overlaps with that in hematologic malignancies. American journal of medical genetics Part A 2017;173:3022-8.
106. Wolk A, Gridley G, Svensson M, et al. A prospective study of obesity and cancer risk (Sweden). Cancer causes & control : CCC 2001;12:13-21.
107. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Archives of general psychiatry 2010;67:220-9.
108. Li Y, Lv MR, Wei YJ, et al. Dietary patterns and depression risk: A meta-analysis. Psychiatry research 2017;253:373-82.
109. Papadimitriou N, Markozannes G, Kanellopoulou A, et al. An umbrella review of the evidence associating diet and cancer risk at 11 anatomical sites. Nature communications 2021;12:4579.
110. Boden JM, Fergusson DM, Horwood LJ. Cigarette smoking and depression: tests of causal linkages using a longitudinal birth cohort. The British journal of psychiatry : the journal of mental science 2010;196:440-6.
111. Gandini S, Botteri E, Iodice S, et al. Tobacco smoking and cancer: a meta-analysis. International journal of cancer 2008;122:155-64.
112. Schuch FB, Vancampfort D, Firth J, et al. Physical Activity and Incident Depression: A Meta-Analysis of Prospective Cohort Studies. The American journal of psychiatry 2018;175:631-48.
113. Friedenreich CM, Ryder-Burbidge C, McNeil J. Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. Molecular oncology 2021;15:790-800.
114. Weinberger AH, Kashan RS, Shpigel DM, et al. Depression and cigarette smoking behavior: A critical review of population-based studies. The American journal of drug and alcohol abuse 2017;43:416-31.
115. Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta oncologica (Stockholm, Sweden) 2009;48:27-33.
116. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC public health 2011;11:450.

117. Swedish Medical Birth Register. 2022. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-medical-birth-register/
118. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. European journal of epidemiology 2016;31:125-36.
119. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. European journal of epidemiology 2017;32:765-73.
120. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. European journal of epidemiology 2019;34:423-37.
121. Ekbom A. The Swedish Multi-generation Register. Methods in molecular biology (Clifton, NJ) 2011;675:215-20.
122. Löfvendahl S, Schelin MEC, Jöud A. The value of the Skåne Health-care Register: Prospectively collected individual-level data for population-based studies. Scandinavian journal of public health 2020;48:56-63.
123. Liu Q, Yin W, Meijsen JJ, et al. Cancer risk in individuals with autism spectrum disorder. Annals of oncology : official journal of the European Society for Medical Oncology 2022;33:713-9.
124. Liu Q, Andersson TM, Jöud A, et al. Cardiovascular Diseases And Psychiatric Disorders During The Diagnostic Workup Of Suspected Hematological Malignancy. Clinical epidemiology 2019;11:1025-34. Originally published by and used with permission from Dove Medical Press Ltd.
125. Liu Q, Song H, Andersson TM, et al. Psychiatric Disorders Are Associated with Increased Risk of Sepsis Following a Cancer Diagnosis. Cancer research 2020;80:3436-42.
126. Liu Q, Adami HO, Reichenberg A, Kolevzon A, Fang F, Sandin S. Cancer risk in individuals with intellectual disability in Sweden: A population-based cohort study. PLoS medicine 2021;18:e1003840.
127. Courchesne E, Gazestani VH, Lewis NE. Prenatal Origins of ASD: The When, What, and How of ASD Development. Trends Neurosci 2020;43:326-42.
128. Courchesne E, Yeung-Courchesne R, Press GA, Hesselink JR, Jernigan TL. Hypoplasia of cerebellar vermal lobules VI and VII in autism. N Engl J Med 1988;318:1349-54.
129. Mandell DS, Ittenbach RF, Levy SE, Pinto-Martin JA. Disparities in diagnoses received prior to a diagnosis of autism spectrum disorder. J Autism Dev Disord 2007;37:1795-802.
130. David F. Bias Reduction of Maximum Likelihood Estimates. Biometrika 1993;80:27–38.
131. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Annals of internal medicine 2017;167:268-74.
132. Cancercentrum. Report of Swedish national quality register for acute myeloid leukemia, 1997-2014. https://www.cancercentrum.se/globalassets/cancerdiagnoser/blod-lymfom-myelom/aml/aml-arsrapport-2016_20170206.pdf. Accessed July 7, 2022.
133. Cancercentrum. Report of Swedish national quality register for lymphoma, 2000-2017. https://www.cancercentrum.se/globalassets/cancerdiagnoser/blod-lymfom-myelom/lymfom/rapporter/lymfomarsrapport2000-2017_1.pdf. Accessed July 7, 2022.
134. Corsello G, Giuffrè M. Congenital malformations. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2012;25 Suppl 1:25-9.

135. Harris BS, Bishop KC, Kemeny HR, Walker JS, Rhee E, Kuller JA. Risk Factors for Birth Defects. Obstetrical & gynecological survey 2017;72:123-35.
136. Sawardekar KP. Profile of major congenital malformations at Nizwa Hospital, Oman: 10-year review. Journal of paediatrics and child health 2005;41:323-30.
137. Hill AP, Zuckerman KE, Fombonne E. Obesity and Autism. Pediatrics 2015;136:1051-61.
138. Koritsas S, Iacono T. Weight, nutrition, food choice, and physical activity in adults with intellectual disability. Journal of intellectual disability research : JIDR 2016;60:355-64.
139. Healy S, Haegele JA, Grenier M, Garcia JM. Physical Activity, Screen-Time Behavior, and Obesity Among 13-Year Olds in Ireland with and without Autism Spectrum Disorder. Journal of autism and developmental disorders 2017;47:49-57.
140. Wallace RA, Webb PM, Schluter PJ. Environmental, medical, behavioural and disability factors associated with Helicobacter pylori infection in adults with intellectual disability. Journal of intellectual disability research : JIDR 2002;46:51-60.
141. Raspini B, Prosperi M, Guiducci L, et al. Dietary Patterns and Weight Status in Italian Preschoolers with Autism Spectrum Disorder and Typically Developing Children. Nutrients 2021;13.
142. Mozos I. Mechanisms linking red blood cell disorders and cardiovascular diseases. BioMed research international 2015;2015:682054.
143. Steptoe A, Kivimäki M. Stress and cardiovascular disease. Nature reviews Cardiology 2012;9:360-70.
144. Dimsdale JE. Psychological stress and cardiovascular disease. Journal of the American College of Cardiology 2008;51:1237-46.
145. Song H, Fall K, Fang F, et al. Stress related disorders and subsequent risk of life threatening infections: population based sibling controlled cohort study. BMJ (Clinical research ed) 2019;367:l5784.
146. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. Immunologic research 2014;58:193-210.
147. Glaser R, Rabin B, Chesney M, Cohen S, Natelson B. Stress-induced immunomodulation: implications for infectious diseases? Jama 1999;281:2268-70.
148. De Hert M, Cohen D, Bobes J, et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World psychiatry : official journal of the World Psychiatric Association (WPA) 2011;10:138-51.
149. Lawrence D, Kisely S. Inequalities in healthcare provision for people with severe mental illness. Journal of psychopharmacology (Oxford, England) 2010;24:61-8.
150. Hernán MA. Invited Commentary: Selection Bias Without Colliders. American journal of epidemiology 2017;185:1048-50.
151. Millard SK, de Knegt NC. Cancer Pain in People With Intellectual Disabilities: Systematic Review and Survey of Health Care Professionals. Journal of pain and symptom management 2019;58:1081-99.e3.
152. Aronowitz RA. When do symptoms become a disease? Annals of internal medicine 2001;134:803-8.
153. Jehn CF, Kühnhardt D, Bartholomae A, et al. Association of IL-6, hypothalamus-pituitary-adrenal axis function, and depression in patients with cancer. Integrative cancer therapies 2010;9:270-5.
154. Iyengar RL, Gandhi S, Aneja A, et al. NSAIDs are associated with lower depression scores in patients with osteoarthritis. The American journal of medicine 2013;126:1017.e11-8.