Psychiatric disease, adverse social aspects, and quality of life in women and men with epilepsy related to pregnancy

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Contents

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Scientific environment

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List of papers

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II. Reiter SF, Veiby G, Bjørk MH, Daltveit AK, Engelsen BA, Gilhus NE. Psychiatric comorbidity, social aspects and quality of life in a population-based cohort of expecting fathers with epilepsy. *PLOS ONE. 2015 Dec 4;10 (12):e0144159.*

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List of abbreviations

ADHD: Attention deficit hyperactivity disorder

AED: Antiepileptic drug(s)

ASRS: Adult ADHD Self-Report Scale

BCE: Before the Common Era

CBZ: Carbamazepine

CI: Confidence interval

EEG: Electroencephalogram

FWE: Fathers with epilepsy

HSCL: (see also SCL): Short version of Hopkins Symptom Check List

LTG: Lamotrigine

LTMD: Life Time Major Depression Scale

MBRN: Medical Birth Registry of Norway

MoBa: The Norwegian Mother and Child Cohort Study

NNCD: Non-neurological chronic disorder

OR: Odds ratio

RSES: Rosenberg Self-Esteem Scale

SCL: (see also HSCL): Short version of Hopkins Symptoms Check List

SCL-A: Short version of Hopkins Symptoms Check List for symptoms of anxiety

SCL-D: Short version of Hopkins Symptoms Check List for symptoms of depression

SPSS: Statistical Package for the Social Sciences

SUDEP: Sudden unexpected death in epilepsy

SWLS: Satisfaction With Life Scale

VPA: Valproic acid

Abstract

Background: Epilepsy occurs in 0.7-1.3 % of the population and affects both genders and all age groups, including women and men of fertile age. Epilepsy is an important cause of disability with consequences for work possibilities, social life and family planning. Psychiatric comorbidity is associated with the condition. The total burden of having epilepsy may affect life quality. Pregnancy is an exciting period for expecting parents, and often women and men are in an optimal phase of life when they decide to have children. However, pregnancy can also be a more vulnerable period for both expecting mothers and fathers.

Aims: In this work it is hypothesized that expecting mothers and fathers with epilepsy are more vulnerable in the period before, during, and after pregnancy than individuals without epilepsy. This can affect both mental health and life satisfaction negatively. To investigate such aspects it is necessary to examine a broad spectrum of factors, such as psychiatric comorbidity, burden of symptoms, socioeconomic conditions and different aspects of life quality. It has been postulated that there is an epilepsy-specific association with such aspects as compared to other chronic disorders. We have elucidated these questions through epidemiological studies of a large population-based cohort.

Material and methods: This work comprises three cross-sectional studies, based on self-reported data from the prospective database of the Norwegian Mother and Child Cohort Study, carried out by the Norwegian Institute of Public Health. Supplementary data on diagnoses and medications were obtained from the Medical Birth Registry of Norway. The study population comprised more than 102,000 pregnancies registered on approximately 95,000 women and 76,000 men recruited from the general population of expecting parents in Norway. From these, more than 700 women and 650 men with epilepsy were identified. The data for the three studies in this thesis was collected in pregnancy weeks 13-17, and 6 and 18 months post-partum.

Results: The frequencies of self-reported psychiatric diseases and psychiatric symptoms were higher in women and men with epilepsy compared to controls, both

prior to and during pregnancy. Adverse social aspects were also more common in epilepsy during and after pregnancy. The association with adverse social conditions seen in persons with epilepsy accounted for some of the differences in psychiatric comorbidity. For some psychosocial aspects the associations were stronger for epilepsy than for other chronic diseases. Several psychiatric diseases showed a higher prevalence when assessed through screening instruments than as self-reported diagnoses. Life satisfaction and self-esteem were lower in expecting women and men with epilepsy during pregnancy, and also in women in the postpartum period and later.

Conclusions: This work demonstrates that both women and men with epilepsy struggle more with challenges concerning mental health and social aspects before, during and after pregnancy compared to persons without epilepsy. Psychiatric problems appear to be underreported, leaving those in need of follow-up for such problems at risk of poorer health outcome and quality of life. This is particularly important to recognize in persons already burdened by a chronic condition such as epilepsy. Expecting fathers' and mothers' mental well-being is important because it may affect delivery and predict postpartum mental health in both parents. Persons with epilepsy being at risk of mental complaints and having socioeconomic problems should be identified prior to pregnancy and offered proper follow up. Screening instruments for mental complaints and quality of life represents an easy method of identifying such problems and indicating the need for further surveillance or intervention. Such instruments could be adjusted to suit prenatal care situations for expecting parents.

1. Introduction

1.1 Historical outline

The word epilepsy is derived from Ancient Greek, "ἐπιλαμβάνειν", which means "to possess", "to seize", or "to afflict" (1). The condition has been known for millennia and is depicted in art (2), and described in ancient texts. Notably, the earliest known description is found in a Mesopotamian text dating to ~ 2,000 years Before the Common Era (BCE) (1). Several famous persons of the ancient world have been said to have had epilepsy including possibly the Greek philosopher Socrates (470–399 BCE) and Roman Emperor Julius Caesar (100–44 BCE) (3). Important figures of later and modern history who reportedly suffered from epilepsy include French leader Napoleon Bonaparte (1769-1821), English writer Charles Dickens (1812-1870), and Russian writer Fyodor Dostoyevsky (1821–1881) (4, 5) who often described seizures in his work (6).

Lack of understanding of the true causes and mechanisms underlying seizures and epilepsy led to superstitious beliefs and social stigmatization of patients, lasting for thousands of years. In ancient Greek, epilepsy was spoken of as "the sacred disease", a divine condition. Rarely, this reflected positive beliefs, such as being blessed by gods, or being provided with abilities to cure illness and disease (1). Mostly, however, persons with epilepsy were believed to be cursed or possessed by evil demons or dark forces, hence names such as "falling sickness" (falling towards Hell) and "lunatic" (from latin *luna*, i.e. controlled by gods of the moon) (1, 7). In his work, "On the Sacred Disease", the ancient Greek physician Hippocrates (460-370 BCE) opposed the beliefs that epilepsy was a spiritual phenomenon (8, 9), and proposed that it was a medical condition, caused by bodily dysfunction and disease. He also noted that heredity could play a role.

Although more than 200 herbs and plants were described as remedies for epilepsy in the 16th and 17th century (10), the most commonly used treatments during the Middle Ages and Renaissance were of religious and superstitious nature (11). Sadly, many people – women in particular – with epilepsy were tortured and killed under the

accusation of sorcery. The concept of epilepsy as a disease originating from the brain first arose in the late 18th and early 19th century (12), but its pathophysiology remained elusive. Persons with epilepsy were commonly admitted against their will to mental asylums and so called "institutions for feebleminded" and almshouses (13). In mental institutions, "epileptics" were often segregated from mentally ill patients, due to the belief that seizures were contagious and could spread to other inmates.

From the middle of the 19th century a more humane and scientific approach to treatment was established, and specialised care units for persons with epilepsy emerged. Around 1860 the National Hospital for the Paralysed and Epileptic in London offered treatment for persons with epilepsy (14). Notably however, epilepsy and "hysteria" were not well differentiated. Other similar institutions included the Bethel Epilepsy Colony in Bielefeld, Germany, and Ohio State Asylum for Epileptics and Epileptic insane (13). The idea behind these institutions was to provide a combination of a safe home and specialized hospital for persons with epilepsy. However, as the eugenics movement established itself stronger in the late 19th and early 20th century, these institutions were gradually transformed to "epilepsy colonies", presented as necessary to keep "epileptics" separated from the rest of the society, as they were considered impulsive, violent and dangerous. Women and men with epilepsy were forbidden to marry and have children, and, taken to the extreme, forced to undergo sterilization (13).

In parallel with these ill-founded segregations and restrictions, important milestones were reached in medical research of epileptogenesis. The taxonomy of epilepsy became more specific, and anatomical and pathological knowledge more detailed in the 19th century. The first works on electric stimuli and brain activity in animal studies appeared around 1870, and in 1873 John Hughlings Jackson (1835-1911), a prominent physician of the 19th century, proposed the following definition for epilepsy: "Epilepsy is the name for occasional, sudden, excessive, rapid and local discharges of grey matter" (12). The history of epileptology shows that several important discoveries followed rapidly after the recognition of the association between electric stimuli and brain activity in the 1870s. Amongst these should be mentioned the first published

animal electroencephalogram (EEG) in 1912 (12), and the first human EEG in 1924, which was met with scepticism, but followed by and confirmed by several studies. Henri Jean Pascal Gastaut (1915-1995) founded the international EEG Federation, and together with his wife, Yvette Gastaut (1918-1989), described the five main patterns of human EEG (12).

In 1857, bromide was introduced as an effective anticonvulsant (15) and was the treatment of choice until it was replaced by phenobarbital in 1912 (12). Other important developments in epilepsy treatment include phenytoin in 1938, carbamazepine (CBZ) in 1953, and sodium valproic acid (VPA) in 1963. From the late 1980s a broad spectrum of newer antiepileptic drugs (AED) has been introduced, including vigabatrin, lamotrigine (LTG) and levetiracetam.

Although research and modern therapy has destroyed many myths about epilepsy, social status and culture still play an important role in the understanding of and beliefs about the condition worldwide. In some societies, epilepsy is still a legitimate reason for divorce, or other kinds of social exclusion, due to lack of knowledge and religious convictions (16-18). As in so many other areas, education is a powerful and important tool to help society overcome irrational and superstitious beliefs about this common, neurological condition.

1.2 Definitions, aetiology and pathophysiology

The International League Against Epilepsy (ILAE) defines epilepsy as a disease of the brain defined by any of the following conditions: 1) At least two unprovoked (or reflex) seizures occurring more than 24 hours apart; 2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60 %) after two unprovoked seizures, occurring over the next 10 years; 3) Diagnosis of an epilepsy syndrome (19).

An epileptic seizure is characterised by abnormal transient and excessive electric impulses between the neurons in the brain (20, 21). The clinical manifestation of this

neuronal discharge is a sudden and temporary phenomenon ranging from almost unnoticeable absences to grave generalised convulsive attacks, and the clinical picture may include altered consciousness, motor, sensory, autonomic, or psychological symptoms (21).

Epileptic seizures are classified into two main groups according to onset and involvement of the areas in the brain: generalised and focal seizures (22). Generalised seizures have a point of origin in the brain, from which an abnormal impulse spreads through bilateral networks to both hemispheres. Both cortical and subcortical areas can be affected, but not necessarily the whole cortex, which implies that generalized seizures can be asymmetric (22). Generalised seizures are further sub-classified on the basis of their symptoms. Focal seizures arise within networks restricted to one hemisphere, either within a limited area, or including most of the affected hemisphere. Epileptic seizures may start as focal and evolve into generalized. A third group is termed "Unknown", under which epileptic spasms is sub-classified. Spasms often occur in series of flexion, extension or both, and last for 1-2 seconds.

Epilepsies are also organized into epilepsy syndromes, characterised by several specific features such as age at onset, seizure type, EEG pattern, and response to drug treatment. The classification is useful in predicting prognosis, establishing aetiology, and providing optimal therapy. Electroclinical epilepsy syndromes are age-specific and include neonatal, infantile, childhood, adolescent, adult, and familial epilepsy syndromes (22, 23). With advances in genetic technology and neuroimaging the various causes for epilepsy are known more accurately. The present terminology by aetiology is 1) genetic, 2) structural, 3) metabolic, 4) immune, 5) infectious, and 6) unknown (22, 23). The organisation and terminology of seizures described here includes the latest suggestions from the ILAE Commission on Classification and Terminology 2011-2013 (23).

ILAE defines status epilepticus as prolonged seizure activity, resulting either from the failure of the mechanisms responsible for seizure termination, or from the initiation of mechanisms which leads to abnormally prolonged seizures (after time point t1). It is a

condition which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures (24). T1 equals 5 minutes, and t2 equals 30 minutes.

Under normal circumstances, neurons interact and communicate in a controlled way through electrical impulses, which are generated over their cell membranes. The cell membrane separates the negatively charged intracellular space of the neuron from the positively charged extracellular matrix. The charges are made up by different concentrations of cations and anions, constituted mainly by an excess of sodium (Na^+) –ions on the outside, while the inside has more potassium (K^+) -ions. This uneven distribution creates an electrochemical gradient, which constitutes the membrane potential (21). The resting potential inside neurons is approximately -77 millivolts in average (depending on the type of the neuron). In the membrane are embedded ligand-gated Na^+ ion-channels, and these open when a stimulus from a neighbouring neuron reaches them. This opening results in an inward current of Na^+, which causes a depolarization of the membrane until the membrane potential reaches a value of about -55 millivolts. This is the electrical threshold, which triggers the rapid opening of voltage-gated ion channels and a further depolarisation. The events so far constitute the rising phase of the action potential, which spreads along the neuron's axon as an impulse and is passed on through synapses to stimulate the next neuron (21). The depolarization state is terminated by a gradual inactivation of the Na^+-channels and the opening of K^+- channels, which causes repolarization through an outflow of the excess K^+-ions from the inside of the neuron. The action potential is usually followed by a transient hyperpolarisation, caused by the delayed closing of the K^+-channels after the resting state has been restored. The ensuing periods are called the absolute and the relative refractory periods. During the absolute refractory period it is impossible to excite the neuron. This state is immediately followed by the relative refractory period, during which a neuron can be triggered if the stimulus is sufficiently strong to reach the threshold.

During an epileptic seizure, the balance between excitatory and inhibitory neuronal signals that normally prevents excessive neuronal discharge is disrupted (25, 26).

Blocking or activating synaptic and/or voltage-gated inhibitory and excitatory channels, respectively, can induce acute epileptic seizures. This state causes neurons to be hyperexcitable and discharge repeatedly. The epileptic seizure results from spreading and synchronisation of this abnormal firing pattern of neurons. The molecular mechanisms underlying this abnormal hyperexcitability and susceptibility to spontaneous seizures in chronic epilepsy are less well understood (26). Genetics play an important a role and have been implicated in both familial and sporadic forms of epilepsy. Several forms of familial epilepsies and epileptic syndromes have been elucidated, many of which have been linked to mutations of genes encoding voltage gated (e.g. Dravet syndrome) (27) or ligand-gated (e.g. nocturnal frontal lobe epilepsy) (28) ion channels. Genetic factors influence also the predisposition to non-Mendelian, idiopathic epilepsy, but most of the heritability of idiopathic epilepsy remains unexplained (29).

1.3 Epidemiology

Epilepsy occurs in all countries and ethnic groups, and in both genders at all ages (30). It is a common neurological disease with a lifetime prevalence varying between 0.7 and 1.3 % on world-wide basis, affecting more than 50-60 million people in total (30-32). The incidence of single occurring seizures is higher than that of epilepsy (33, 34). Some of the variance in estimated prevalence is due to methodological differences and study design. However, there are distinct geographical variations in prevalence, with highest rates in South America and Africa, ranging from approximately 1.2 - 7.0 % (35, 36), compared to 0.4 - 1.0 % in Western and some Asian countries (31, 37, 38). These prevalence numbers do not distinguish between lifetime prevalence and prevalence of active epilepsy. The higher numbers in developing countries and poor regions of the world is mainly due to more risk factors and poorer health services (39). Prevalence estimates also vary internally in countries according to socioeconomic status, with a higher frequency in poor socioeconomic classes (40, 41). The estimated prevalence in lower-income economies and resource-poor countries may even be

underestimated due to lack of registration and premature deaths (42). Epidemiological studies on familial risk of epilepsy are quite extensive, but the results have been inconclusive or restricted by methodological limitations (43). The rapidly expanding number of genetic studies in the field of epileptology should improve our understanding of hereditary aspects.

The incidence and prevalence of epilepsy vary with age. The incidence rate has a bimodal distribution, peaking in early childhood and after 50 years of age (44). The prevalence in the older age group is higher because of increased susceptibility to risk factors, such as stroke, traumatic injuries and brain tumours. In contrast to these findings, studies from developing countries have shown a higher prevalence in younger age groups of adolescents and young adults (45), probably due to premature deaths in adults. Some types of epilepsies have a typical age of onset and are classified accordingly, such as the electroclinical syndromes with myoclonic encephalopathy in the neonatal period (<44 weeks of gestational age), West syndrome in infancy (<1 year), benign epilepsy with centrotemporal spikes during childhood (1-12 years), and juvenile myoclonic epilepsy (12-18 years) (22). Some of these syndromes show a spontaneous remission.

Focal seizures are more common than generalized seizures in developed countries, and most common in the elderly (46-48). Focal seizures can be mislabelled as generalized due to secondary generalization following a subclinical and/or unnoticed focal start. Therefore precise diagnosis requires neurophysiology in addition to clinical history and examination. In a study using EEG as a supplement to clinical evaluation, the proportion diagnosed with focal seizures increased from 35 % to 50 % (49). In resource-poor countries generalized seizures dominate (36, 50), but the distribution may reflect underdiagnosis due to poor EEG availability (51).

As the definition and classifications of epilepsy change this may affect comparisons with previous epidemiological studies on gender differences (19, 52). Overall findings suggest that incidence and prevalence of epilepsy are slightly higher in men than women (40, 44, 53, 54). Although absolute gender differences are minor, findings

suggest that different epilepsy types have different gender susceptibility (55). The difference appears to be consistent even after considering risks of head injuries, stroke and infections in the central nervous system, which are all more common in men (54, 56). A recent review paper points out gender differences regarding several aspects, such as epidemiology, cerebral anatomy, seizure location and seizure semiology (53). The higher prevalence seen in men is partly due to a higher frequency of partial seizures (57). One early explanation for this observation was proposed by Taylor *et al.* (58). They suggested that a slower, and thereby prolonged, cerebral maturation in boys exposed them to a longer time period of vulnerable development, in which a lesion might occur and produce an epileptic focus. Another explanation, supported by animal models in rats, is that males are more vulnerable to seizures when a lesion is present compared to females (59). Although the terms "idiopathic" and "symptomatic" are no longer recommended by ILAE (22), until recently they were used when describing generalized idiopathic epilepsy and symptomatic localization-related epilepsy, both types seen more often in women (55). Some epilepsy syndromes have different frequencies and even clinical features depending on gender (54). Sex hormones are believed to play an important role in gender epileptology, and the theory is supported by findings that menstrual cycle affects seizure frequency, and that gender differences are most pronounced in adults before menopause in women (55). One of the most important gender differences to be considered in epilepsy is related to pregnancy, which is discussed in a later section.

1.4 Comorbidity and mortality in epilepsy

Comorbidity refers to the coexistence of two or more medical conditions in the same person. Comorbidity in epilepsy is high relative to the general population, and includes both psychiatric and somatic conditions (60). The relevance of each comorbid disease is important to understand, as they influence and may predict seizure activity, prognosis and life satisfaction. Several comorbidities are undetected or underreported

after a first seizure, and this may cause a delay in intervention and prevention of further seizures (61).

Among somatic comorbidities a number of epidemiological studies have found migraine, diabetes, asthma and arthritis to be associated with epilepsy (62-64). The distribution of the comorbidities according to age, gender and socioeconomic aspects is often equal to the general population, however, generally more frequent in epilepsy (60). Some somatic comorbidities show a higher frequency in epilepsy without an obvious causative explanation, while others are strongly associated with epilepsy, such as stroke, neoplasms, and Alzheimer's disease. This is not surprising, as these can represent the cause that provokes a first seizure in epilepsy. Other conditions may occur as side effects from AEDs, including heart arrhythmias, asthma and osteoporosis-tendency (63, 65). Mechanisms for the relationship between epilepsy and its comorbidities, including genetic, biologic and environmental aspects, are discussed in several thorough review studies (60, 66).

Symptoms and signs in both epilepsy and psychiatric disease have their origin from the same organ, the brain. It is therefore not surprising that several psychiatric disorders are associated with epilepsy, and the risk of psychiatric comorbidity is extensively documented in both children and adults over decades (62, 67-69). Depression is the most common and anxiety the second most common psychiatric comorbidity in epilepsy, with studies showing depression prevalence ranging from 30 to 60 % in persons with epilepsy (70). However, these numbers probably include selected patient groups with a greater disease burden, recruited from specialized institutions. Nevertheless, also population- and community-based studies show high depression rates in epilepsy, and suicidal numbers are also increased (67, 69, 71). In addition to mood disorders, anxiety and phobias are increased in persons with epilepsy, and so are psychosis and schizophrenia (67, 70), with a more complex clinical picture of coexisting psychiatric disorders in epilepsy syndromes (72). Although the association between epilepsy and psychiatric disease is extensively documented, the underlying mechanisms are not well understood. Some theories suggest a shared underlying aetiology, or a bidirectional relationship, with epilepsy

causing psychiatric disease or vice versa (73-75). For instance, in a population-based case-control study, Adelöw *et al.* found an increased risk of seizures after a hospital-based diagnosis of psychiatric disorders (76). Psychiatric comorbidity complicates epilepsy treatment. Conversely, there are several challenges in treating psychiatric comorbidities in epilepsy, including risk of side effects, therapy compliance, and managing and monitoring polytherapy.

Findings suggest a two- to three-fold increased mortality rate in epilepsy (77), some studies show even higher numbers (78). Somatic and psychiatric comorbidities increase mortality in epilepsy significantly, and low socioeconomic status adds to this risk (78, 79). Multi-morbidity can delay diagnosis and treatment, complicate therapy, and increase side effects from polypharmacy. Also direct effects from epilepsy *per se* cause premature mortality. Sudden unexpected death in epilepsy (SUDEP) accounts for less than half of epilepsy-related deaths, but SUDEP-numbers may be underestimated (80). SUDEP does not include status epilepticus, which is another direct cause of premature death in epilepsy. The mortality rate of status epilepticus varies between 10 and 22 % (32). The most important prognostic factors in SE include underlying etiology/disease, pre-existing epilepsy (versus *de novo* SE) and age. Further epilepsy-related death-causes are traffic accidents, drowning and other accidents due to seizures. A recent review based on several Western studies suggests that the increased epilepsy mortality is mostly due to underlying causes of the epilepsy, and not seizures (77)

1.5 Socioeconomic aspects and quality of life

As for psychiatric comorbidity, there is a bidirectional relationship between epilepsy and adverse socioeconomic status; persons with epilepsy experience more socioeconomic problems, and the incidence and prevalence of epilepsy are higher in low-economy societies and groups (39-41). This implies that epilepsy has a negative effect on social and economic status, but also that psychosocial and economic challenges may worsen epilepsy.

Children with epilepsy have more problems with memory and school achievements, with high seizure activity predicting worse outcomes (81-83). They have fewer close friends and experience more socioeconomic disadvantages compared to peers without epilepsy (84), both of which are risk factors for low health-related quality of life and for behavioural problems (85, 86). Moreover, fear of seizures can lead to overprotective behaviour from parents, preventing children from creating important social relationships and skills. Parents' worries may also influence the child and provoke feelings of insecurity and anxiety (85). Growing up with the impression of having disabling health issues, or just feeling different from peers, can be associated with shame, and some keep the condition a secret to avoid being treated differently (87). Epileptic seizures are often associated with feelings of loss of control and social stigma (18).

The basis for coping with social and academic challenges later in youth and adolescence is formed during early childhood. It is therefore not surprising that teenagers with epilepsy show lower academic achievements, have more social problems, and report more worries about their own future regarding relationships and work opportunities (87, 88). A follow-up study of young people with epilepsy aged 11-17 years over four years, showed that academic achievement did not improve, even though their medical condition improved (89). The authors suggested that the children and youths had missed out on important information early in school, or that seizures had an irreversible effect on their learning abilities. Social acceptance and group identification is particularly important in youth, while peer-rejection can be devastating. Obtaining social acceptance may include indulging in risk-related behaviour, such as alcohol intake and substance abuse, or skipping the AED-treatment (88). This can destabilize the epilepsy and trigger seizures. Proper information in order to prevent seizures is important. A qualitative study on SUDEP showed that young people with epilepsy preferred to get information on this serious subject early, and they did not show long-term increased anxiety due to this (90).

Most people with epilepsy are expected to develop normally from childhood to adults, and to live normal lives. Challenges from childhood and adolescence may, however,

have long-term effects into adult life (91). Recurrent seizures and lack of satisfying treatment usually affect daily living. Epilepsy in adults is associated with lower educational level and income, unemployment, disability, poorer social network, absence of a life partner, and increased divorce rates compared to adults without epilepsy (91-93). Having a job, a social network and a life partner are in general important predictors for quality of life and mental health, while unemployment is associated with loss of social network and depression. Living with a chronic disease such as epilepsy regularly implies restrictions to daily life activities at work and home, and in leisure activities (92). Epilepsy-specific concerns include car-driving, restrictions of work possibilities due to seizure danger, such as offshore-jobs, transport driving, etc., worries about AED-side effects, and family planning. Having a partner is shown to be particularly beneficial for coping skills and feeling of security in adults with epilepsy (93), and social support is important for AED-adherence (94).

1.6 Treatment of epilepsy

Prognosis of epilepsy is variable, depending of type of seizures and aetiology, but often it is good (95). In addition to absence of organic brain damage and mild and infrequent seizures, the most reliable predictor of a good prognosis is adequate response to early AED treatment (95, 96). Immediate AED treatment after a first seizure is likely to reduce the risk of new seizures occurring within the next two years, however it does not seem to improve long-term seizure remission prognosis (97). In many instances information on risk factors and non-drug preventive measures are tried as intervention before AED-treatment is initiated. In each patient recurrence risk must be weighed against potential adverse effects from AEDs.

As the cause of epilepsy is often unknown, the treatment is mostly symptomatic, aiming at preventing epileptic seizures and sub-clinical epileptic activity. Between 50 and 70 % of persons with epilepsy become seizure free with modern, optimal AED-monotherapy (97-102). For a smaller group, more than one AED is necessary, which requires extra attention to side effects, drug interactions, and monitoring of serum

levels of AEDs (103, 104). AEDs are sometimes categorised into newer AEDs, such as gabapentin, LTG and oxcarbazepine, and older AEDs, for instance VPA, CBZ and phenytoin, with older AEDs referring to medications introduced before 1993 (105, 106). For most AEDs the complete mode of action is not clear. Many AEDs work by blocking ion channels, stimulating inhibitory γ-aminobutyric acid (GABA)-receptors, or blocking excitatory glutamate receptors (107, 108). Some AEDs, such as LTG, CBZ and phenytoin, bind to the ion channels and stabilize them in their inactivated states. GABA-receptor stimulation can be induced by decreasing GABA-metabolism (vigabatrin), inhibiting reuptake in the synapse (tiagabine), increasing GABA-production (gabapentin), or by directly stimulating the GABA-receptor by binding to it (benzodiazepines). Some AEDs have more than one mode of action. VPA, for instance, blocks voltage-dependent Na^{+}-channels, but is also suggested to block Ca^{2+}-channels, and additionally to elevate GABA-levels, and decrease the level of the excitatory amino acid aspartate. Several AEDs work by mechanisms that are not fully understood or are unknown (107, 108). A 2013 special report from ILAE summarises the evidence for long-term efficacy and effectiveness of AED-monotherapy in various seizures and syndromes (109). For optimal treatment, the report stresses the importance of individual evaluation in each case of epilepsy. Significant issues to consider are age, gender, syndromes and seizure type, comorbidity, co-medications, including contraceptives, and pregnancy. Concern about side-effects from long term AED-treatment leads to a discussion about discontinuing treatment in seizure free patients (110-112). Teratogenicity and cognitive influence from AED, especially in developing children, are important issues, but must be weighed against recurrence risk in each individual case (113, 114). Even with gradually and carefully withdrawal there is a considerable risk of seizure relapse within the first year, varying according to epilepsy type (111, 115).

Therapy strategies in epilepsy include life style interventions such as proper sleep hygiene and avoidance of alcohol and other known triggers. Another option is ketogenic diet, with high fat and low carbohydrate content (116). In some cases, vagus nerve stimulation should be considered, for instance in children with refractory epilepsy (117). Some patients with severe therapy-resistant epilepsy undergo

neurosurgery in order to remove the epileptogenic region (118, 119). An increasing body of literature gives a glimpse into future potential therapies, including gene therapy and other personalised aspects (120, 121).

1.7 Epilepsy during and after pregnancy

Epilepsy affects people in all age groups, including women and men of fertile age. The condition implies extra challenges during the vulnerable situation of pregnancy (122). In most cases, pregnancy proceeds without complications. However, even without the extra burden imposed by a chronic condition, pregnancy implies physiological changes, with hormonal and physical alterations, as well as psychological and social changes. Pregnancy is associated with increased risk of hypertension, diabetes, thromboembolism, musculoskeletal complaints, leg cramps, and varicose veins, to mention some. Preeclampsia occurs in as many as 3-5 % of all pregnancies (123), and gestational diabetes is reported in up to 14 % (124). In addition some experience a worsening of pre-existing chronic conditions, such as asthma (125). In women with epilepsy, several pregnancy-related risks are increased compared to women without epilepsy, including pregnancy hypertension, preeclampsia, bleeding during pregnancy, and preterm delivery (126). Birth complications, such as induction of labour, caesarean section, and excessive bleeding postpartum, are also more common in women with epilepsy (127). Epilepsy is associated with more adverse birth outcomes for the child, such as malformations and small for gestational age, though mainly related to AED-treatment, in particular VPA (106, 128). However, studies on obstetrical complications in epilepsy are to some degree contradictory concerning risk estimates, with other studies showing minor or no difference between women with and without epilepsy, and this raises the question about true risks in epilepsy and pregnancy (129).

In the general population, 7-20 % of pregnant women in high income countries experience depression (130), with less than 20 % receiving treatment (131). Perinatal anxiety occurs in 4-39 % of women (132), while postpartum depression varies between 7 and 30 % across high- and low resource countries (130). Antenatal

depression and anxiety have been shown to be major risk factors for recurrent depression postpartum (133, 134), and poor partner relationship, stressful life events and worries about the baby are important triggers for both depression and anxiety.

Women with epilepsy face specific challenges during pregnancy concerning seizures and AED-treatment, and these two aspects must be weighed against each other. Uncontrolled seizures can harm both the mother and the foetus (122, 135). AED-treatment, on the other hand, may expose the foetus to teratogenicity, with particularly high risks for VPA and AED-polytherapy (128, 136, 137). Some AEDs are associated with foetal growth restrictions and birth defects (138), but several are considered safe to use during pregnancy, and breastfeeding is generally encouraged (139). Nevertheless, AED-use during pregnancy may cause worries and a feeling of guilt in the mother. AED-use during pregnancy demands careful monitoring of serum levels and doses, as changes in hormones and body fluid-balance affects AED-metabolism (140). Change of therapy dose constitutes a risk of epileptic seizures, and therapy should be optimized before pregnancy (122). Although many women may appreciate extra follow-up during pregnancy, extra health controls with monitoring of AED-levels may cause tension and feeling of being ill instead of pregnant and healthy.

Fathers to be do not go through the same physiological changes or physical risks as pregnant women, and expecting fathers with epilepsy are not at risk of drug complications in relation to pregnancy like pregnant women are. However, fathers to be are increasingly expected to participate during and after pregnancy, and newer studies suggest that expecting fathers also experience anxiety and depression during pregnancy (141), with a decline in emotional health after pregnancy, and reports of postpartum depression in up to 10 % (142, 143). Both men and women who experience psychiatric symptoms during pregnancy often have prolonged depressive symptoms post-partum (144).

Given the extra risks and challenges faced by expecting parents with epilepsy they may fare worse than peers without epilepsy in the period during and after pregnancy. Studies undertaken so far on mental health and quality of life, including social aspects,

in expecting mothers with epilepsy have been insufficient or contradictory, and studies on fathers to be with epilepsy have been missing. Parents' well-being and life satisfaction have consequences for their children. Thus in my opinion, it was necessary to conduct studies that illuminate these aspects further.

2. Aims

The work in this thesis aims at showing important aspects of psychosocial conditions and quality of life in individuals with epilepsy during and after pregnancy through epidemiological studies of well-defined cohorts. We hypothesised that given the already known risks in non-pregnant persons with epilepsy, these risks may be more pronounced also during and after pregnancy in an otherwise young and healthy epilepsy population. We chose to include fathers as they increasingly are expected to participate during pregnancy and, in some countries such as Norway, are both obliged and expected to take paternity leave. Since there are obvious differences between women and men regarding biological and physiological changes in relation to pregnancy, we chose not to perform any direct comparisons between the genders. The study and determination of risks in a large, representative patient cohort from the general population can help guide health authorities in giving public recommendations and where to invest health resources. Also, women and men with epilepsy are entitled to know about potential risks associated with their condition in order to get proper support and follow up if needed.

The main aims of this work were to describe the following in pregnant women and men prior to, during and after pregnancy:

- To determine prevalence and risks of psychiatric comorbidity close before and during pregnancy in women and men with epilepsy.
- To describe adverse socioeconomic aspects and life events during and after pregnancy in persons with epilepsy.
- To examine quality of life during and after pregnancy in both genders with epilepsy.
- To assess the impact of epilepsy by comparing risk of adverse outcomes with non-neurological chronic diseases.

3. Material and Methods

3.1 Data material

3.1.1 The Norwegian Mother and Child Cohort Study

The Norwegian Mother and Child Cohort Study (MoBa) is an ongoing prospective population-based study, organized as a large database. It was authorized by the Norwegian Data Protection Authority, and carried out by the Norwegian Institute of Public Health (145). The study inclusion was initiated in June 1999 and lasted until December 2008, with continued follow-up of the included children and their mothers in the years after delivery. Information on more than 100,000 pregnancies was gathered, with the aim of testing specific hypotheses about disease causes. Norwegian-speaking pregnant women and their partners at hospitals, and maternity units with more than 100 births annually, from all over Norway were invited to participate prior to a scheduled routine ultrasound examination in pregnancy weeks 18-19. The invitation and first questionnaires (questionnaire 1) were sent out in weeks 13-17 of pregnancy. The response rate among those invited was 41 % (146). Data consists of self-reported information, and biological material from blood samples. Fathers were included from year 2000, and participated with only one questionnaire obtained in pregnancy week 15, whereas mothers were followed up with new questionnaires in pregnancy week 22 (questionnaire 2) and 30 (questionnaire 3), and thereafter 6 (questionnaire 4), 18 (questionnaire 5), 36 (questionnaire 6) and 60 months after birth (questionnaire 7). For women with multiple pregnancies, each birth outcome and child was followed up separately with the different questionnaires after birth. The self-reported data in MoBa includes information on pregnancy- and birth-related conditions, illnesses, medications, socioeconomic data, dietary factors, life style matters, environmental exposures, and information on the baby and later development of the child. The only exclusion criterion from MoBa was miscarriage prior to the routine ultrasound examination at pregnancy weeks 17-19. MoBa now includes data from more than 102,000 unique pregnancies registered on 95,000 women and 76,000 men. It should be noted that the estimated pregnancy weeks in MoBa-questionnaire 1

are described differently in paper I and III, with weeks 13-17 and 15-19 respectively. This is due some variation in the sources describing MoBa (146, 147).

Each pregnancy in MoBa has a unique identification number, which is used in the subsequent follow-up questionnaires. The identification number in the files can be used to link MoBa to other health data. Data files are released without names or personal identity number of the participants. Qualified researchers and research groups in Norway, as well as international researchers collaborating with Norwegian researchers, can apply for access to data files from MoBa (148). All research projects based on MoBa must follow specific guidelines and be approved by a Norwegian regional committee for medical and health research ethics before access can be given to the data files.

The qualified data files from MoBa have been updated several times during the study period. The two first studies in this thesis, paper I and II, were based on version 5 of the MoBa files (MoBaV5) released in August 2010. The third and last study, paper III, was based on an updated version 8 of the MoBa files (MoBaV8) released in February 2014. Data in all three studies included information from the questionnaires, but not biological material. Paper I included information from the women's questionnaire 1, paper II was based on the men's questionnaire, and paper III included information from the women's questionnaires 1, 4 and 5.

3.1.2 Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) is a national, compulsory health registry, established in 1967 and managed by the Norwegian Institute of Public Health (149, 150). All births at maternity units, and home births, in Norway are required to be registered in MBRN. The registering of births is further ensured through a linkage to the National Population Register of Norway. During pregnancy, health and demographic information is registered by midwifes or general practitioners at the prenatal controls. During labour midwifes and physicians record information on

delivery, complications and birth outcomes (Appendix III). The data in MBRN is used for surveillance, research, providing information to healthcare professionals, and compilation of population statistics. Information on maternal health before and during pregnancy, as well as birth and socioeconomic conditions are included. Pregnancies terminated before week 12 are not included in MBRN. Researchers and health personnel can apply for use of data within the MBRN's regulations. As with MoBa, data from MBRN can be linked to other population and health registries through an anonymous coding system.

Data files from MBRN were updated during the study period. Paper I and III included data files from MBRN-version 3.3.0 and 4.1.0, respectively. Information on epilepsy diagnosis, AED-treatment and smoking from MBRN was used to supplement information from MoBa.

3.2 Study population

The study unit in this work was pregnancy, and each pregnancy was registered with a unique identification number. This means that the same women and men could be enrolled more than once during the inclusion period. In our studies, we chose to call each unique pregnancy or unit a "woman" or a "man".

There is a slight discrepancy between the size of the study populations presented in paper I and III during pregnancy related to questionnaire 1, with 106,935 and 102,265 pregnancies respectively. MoBaV5 contained 101,639 pregnancies which were merged with MBRN version 3.3.0., comprising 106,935 pregnancies. The 5,296 extra pregnancies from MBRN where from women who consented to participate in MoBa, but never returned questionnaire 1. Since no data were registered for the extra pregnancies, these had no impact on the analyses or results. Numbers of participants are therefore described below as presented in the papers.

Due to the updating of files from MoBaV5 to MoBaV8 in paper I and III, respectively, the number of participating women increased from 101,639 to 102,265. The number in

the epilepsy group increased correspondingly from 711 to 719. This increase was partly explained by the delayed return of participation consent forms for those who had filled out MoBa-questionnaire 1 without returning the consent form (147). Additionally, after year 2000 the Regional Committees for Medical and Health Research Ethics and the Norwegian Data Protection Authority decided that if the invited persons had donated a blood sample or returned a questionnaire they could be included in the study (147). Consequently the number of participants increased in the updated MoBa-versions.

At the start of this PhD-project *a priori* power analysis was performed to estimate statistical power to detect risk estimates in the epilepsy group regarding psychiatric comorbidity. The calculation was based on a two-tail test with alpha error level of 5 % and a reference and an epilepsy group with 100,000 and 700 women respectively. The prevalence of psychiatric disorders in the reference and epilepsy group was estimated to be 10 % and 15 %, respectively. This gave a statistical power of 98.8 %.

3.2.1 Paper I

This study was based on data from the women's MoBaV5 questionnaire 1, and from MBRN-version 3.3.0. The two datasets were merged and included information from a total of 106,935 pregnancies (women) in paper I.

A diagnosis of epilepsy was defined through the following criteria:

1. A self-reported previous or current diagnosis of epilepsy through a predefined specific question on epilepsy in MoBa.
   or
2. A diagnosis of epilepsy in both MoBa and MBRN, and AED-use registered in MBRN.

AED-use was identified through the following criteria:

1. Self-reported previous or current AED-use under the predefined specific question on epilepsy in MoBa.
   or
2. Having ticked off the predefined specific question on epilepsy and filled out information on AED-use in a free-text area in the questionnaire.
   or
3. A diagnosis of epilepsy in both MoBa and MBRN, and AED-use registered in MBRN.

A total of 711 pregnancies were identified in pregnant women with epilepsy. The pregnancies were referred to as "mothers" or "women" in the study. AED-use was registered in 329 women. All women without epilepsy in MoBa (n = 106,224), served as a reference group. The primary analyses included all recorded pregnancies. The 711 pregnancies were registered for 634 unique women during the whole inclusion period. To account for potential effects of repeated measures in the same woman, the analyses were also done for the 634 first pregnancies separately. The estimates of risks were practically the same for first pregnancy only and all pregnancies, and strengthened our conclusions (supplementary tables in paper I). Thus, we have shown that the effect of repeated pregnancies in the same women had no significant effect on our main outcomes.

3.2.2 Paper II

Data were obtained from the expecting fathers' MoBaV5-questionnaire, filled out during their partners' pregnancy week 13-17. All 76,335 men in MoBaV5 were included.

Epilepsy, AED-use, and treatment-requiring non-neurological chronic disorders (NNCD) were defined as follows:

1. Epilepsy was defined by self-reported ticking-off a predefined question about a diagnosis of epilepsy.

2. AED use was registered according to ticking off the predefined specific question on epilepsy and in addition filling out information on AED-use in a free-text area in the questionnaire.
3. A reference group with NNCD was selected from the self-reported ticking-off a predefined question on a diagnosis of diabetes, rheumatoid arthritis, heart disease or asthma and in addition filling out information on drug treatment related to these diseases in a free-text area in the questionnaire.

Altogether 658 men were registered with a diagnosis of epilepsy, of which 243 used AED. 8,475 men were identified to have a drug-requiring NNCD. The reason for choosing drug dependent NNCD, and not NNCD without treatment, was to avoid comparing a "too healthy" chronic disease group to the references without epilepsy and to the epilepsy group.

3.2.3 Paper III

Our third study included data from questionnaire 1 (pregnancy weeks 13-17, 4 (6 months postpartum) and 5 (18 months postpartum) from MoBaV8 and MBRN-version 4.1.0. Epilepsy and AED-use were identified from MoBa questionnaire 1 and MBRN as described for paper I. All singleton births and the first child in those with multiple pregnancies were included from MBRN and MoBa questionnaire 4 and 5. In order to avoid any influence of a new pregnancy on the outcomes at time point three (18 months postpartum), women who were pregnant again at this time point were excluded (n = 10,648, of whom 72 had epilepsy). The four datasets were merged, yielding a study population of 102,265, 88,090 and 64,443 women at pregnancy weeks 13-17, and 6 and 18 months postpartum, respectively. Of these, 719, 564 and 409 had epilepsy, respectively (Paper III, Figure I).

3.3 Variables and measures

3.3.1 AED use

Data on AEDs were coded according to the Anatomical Therapeutic Chemical Classification System, consisting of a five-digit number (151). AED use during pregnancy in women, and during the past six months in men, was registered for the epilepsy groups. AED use was stratified into four groups: polytherapy (use of two or more AEDs simultaneously), and three separate monotherapy groups: LTG, VPA, and CBZ. Other anticonvulsants registered as monotherapy included levetiracetam, topiramate, oxcarbazepine, clonazepam, phenytoin, phenobarbital, gabapentin, primidone, clobazam, and unspecified AEDs.

3.3.2 Predefined self-reported psychiatric diagnoses

Three predefined questions on eating disorders, anxiety and depression were available for our studies from the women's questionnaire 1 during pregnancy. The diagnoses were assessed by the women ticking off in a check box for a diagnosis prior to and/or during pregnancy. Four predefined questions from the men's questionnaire included attention deficit hyperactivity disorder (ADHD), bipolar disorder, anorexia/bulimia/other eating disorder, schizophrenia, and unspecified (other) psychiatric disorders.

3.3.3 Screening tools and symptoms

Screening tools from the questionnaires were for our studies constructed into dichotomous variables. In paper III, some items were additionally used as continuous variables. To avoid potential sample distortions, a maximum likelihood estimation procedure was applied to impute missing values for all the scores (152). Scores with ≥ 20% missing data were excluded. The screening tools used are summarized below and a full description of these tools is presented in Appendix I.

- ***Life Time History of Major Depression (LTMD)*** (paper I and II): This represents a

validated screening tool for major depression (153), which meets the criteria in the classification system Diagnostic and Statistical Manual of mental disorder (DSM) III if I) at least three out of six symptom items are endorsed, II) one of these symptoms is the first one on the list (felt depressed), III) three types of symptoms occurred simultaneously, IV) the symptoms were not caused by an external event. The men's questionnaire did not include item IV.

- ***Short version of Hopkins' Symptom Checklist (SCL)*** (paper I-III): This represents a validated scale for present depression and anxiety, originally containing 25 items (154). SCL was available with 5 items from the women's questionnaire 1, with a correlation of 0.92 with the original scale (155). Mean score > 1.75 was set as cut off value for significant scores on this SCL-scale with 5 items. SCL in the men's questionnaire (paper II) included 8 items, which were subdivided into two 4-item scales for present symptoms of anxiety (SCL-A,) and depression (SCL-D) respectively. SCL-A was constructed from item 3, 4, 5 and 6. SCL-D was constructed from item 1, 2, 7 and 8. Mean score > 1.75 was set as cut off value for significant scores on the two SCL-scales with 4 items.
- ***Short version of the World Health Organization's (WHO) Adult ADHD Self Report Scale (ASRS)*** (paper III): The original screening tool includes 18 items. In both epidemiological community surveys and in clinical studies, the short version of ASRS with 6 items has shown good internal consistency, with Cronbach's alpha (CA) varying between 0.63 and 0.72 (156).
- ***Short version of Rosenberg's Self-Esteem Scale (RSES)*** (paper II and III): The original version comprises 10 items (157), whereas the validated short version includes 4 items and has a correlation of 0.95 with the original scale (158).
- ***Relationship Satisfaction Scale (RSS)*** (paper III): A 10-item scale that was constructed for MoBa, based on established scales for marital and relationship satisfaction (159). RSS was used for assessing partner support and has shown good psychometric qualities and high internal consistency with CA varying between 0.89 and 0.91 (160).
- ***Satisfaction With Life Scale (SWLS)*** (paper II and III): This is psychometric 5 item scale evaluated for use cross-culturally and for different age groups (161), with score

≤ 9 defining low satisfaction with life. SWLS was used to assess global satisfaction with life in paper II, and at pregnancy weeks 13-17 and six months postpartum in paper III.

- ***WHO's Quality of Life Instrument-short version (WHO QoL-BREF)*** (paper III): This instrument includes 26 of 100 items from WHO QOL-100, and has been evaluated as suited for epidemiological studies (162, 163). In paper III one specific question on global QoL (from now on referred to as QoL), and one question on global quality of somatic health from WHO QoL-BREF were used separately. Both questions had a scale ranging from 1-5. QoL was used to assess global satisfaction with life at18 months postpartum because SWLS was not available at this time point.
- ***The General Efficacy Scale (GSE)*** (paper III): GSE is a 5-item validated scale used cross culturally. Previous evaluation through meta-analysis has acknowledged the scale as a reliable tool for measuring a person's skills of coping with challenging situations (164).
- ***Work strain*** (paper III): Work strain was measured by constructing a variable from 6 questions describing daily work situation. This is not a formally validated scale. Generally, CA should preferably be > 0.70 for internal reliability (165). For Work strain we accepted a CA result of 0.59.
- ***Social support*** (paper III): Three independent questions were used separately, the two first with scales graded 1-3, and the third graded 1-5 (Appendix I).
    - "No friends": Defined as reporting no friends except for the life partner.
    - "Reduced social contact": Meeting or talking on the phone with people other than their partner less than once a month.
    - "Feeling lonely": A person was said to be "feeling lonely" when answering "usually" or "almost always" to the question "Do you often feel lonely".

With no clear recommendations in the literature for cut-off levels for the screening tools, these were defined as follows: Mean – 2 SD was set as cut off for low scores on QoL, RSS, RSES, GSE, and quality of somatic health, while mean + 2 SD was set as cut-off for high scores on work strain. As the scores on RSS were generally very high,

we used mean – 1 SD to define low RSS. Strict cut-off levels defined in this way should improve construct validity for assessing true complaints and impairment (166).

3.3.4 Demographic and socioeconomic characteristics

In paper I-III maternal and paternal information on demographic and social aspects included: Education ≤ 12 years, low income, no income, financial insecurity (not being able to handle unexpected expenses of 1,180 Euro in a month), unemployment due to disability, single parenting, smoking during pregnancy, alcohol use during pregnancy (pregnant women ≥ 1 occasion per month, men > 10 units/week), and any narcotics use before pregnancy. Narcotics included cannabis, amphetamine, ecstasy, cocaine, and heroin. Amphetamine abuse was assessed through specific questions on drug abuse separate from questions on drug therapy in relation to ADHD. Low income was defined as a household income per consumption unit < 60 % of the median for the country (167).

As the MoBa questionnaires were modified several times during the inclusion period, some of the variables were available only from later questionnaire versions. Numbers were therefore lower than total number of participants in some analysis.

3.3.5 Adverse life events

In paper III, adverse life events were recorded through 11 questions available 6 and 18 months postpartum, "Have you experienced any of the following (events) during the past 12 months": 1) Problems at work, 2) Financial problems, 3) Divorce/separation, 4) Conflicts with family/friends/neighbours, 5) Concerns about the baby, 6) Serious personal injury/illness, 7) Close relative being injured/ill, 8) Involved in traffic accident/fire/robbery, 9) Lost someone close, 10) Forced into sexual activity, 11) Exposed to physical violence. The question on sexual abuse was only included for the men, as this question had already been addressed in another publication regarding

MoBa-women, not included in this thesis (168).

3.4 Statistical Methods

The software Statistical Package for the Social Sciences (SPSS) IBM version 18.0 and 21.0 (SPSS Inc., Chicago, IL, USA) was used in all analyses.

Dichotomous variables were analysed by Pearson's chi-square test, and by Fisher's exact test for cross-tabulations with expected cell count less than five. The results of comparisons between the epilepsy and reference groups were presented as crude frequencies and unadjusted odds ratios (OR) with 95 % confidence interval (CI) and corresponding p-values. Two-sided p-values < 0.05 were considered statistically significant in all analysis of our work. Estimates for continuous variables were calculated through independent-samples t-test, and presented with mean score and corresponding SD and p-values. We used odds ratio as an estimate of relative effect. Due to the low prevalence of epilepsy in the general population (approximately 0.7 %) the "rare disease assumption" should be applicable for epilepsy (169), and the OR should closely reflect the risk ratio.

To assess the potential impact of classical confounding factors and adverse socioeconomic aspects, significant risks in the epilepsy group were further analysed with unconditional logistic regression analyses for dichotomous variables. Results were presented as adjusted OR with 95 % CI and corresponding p-values. Multiple linear regression was performed for continuous variables. In paper III, some of the independent, dichotomous variables were based on screening tools with variable scales, as described previously. The strength of correlation (B) in these analyses was therefore not comparable in all aspects, but indicated the direction of the correlation. To assess the associations between global life satisfaction and various life conditions for the epilepsy group in paper III, separate linear regression analyses were performed for this group. In order to estimate the effect of epilepsy on global life satisfaction without over- or under adjustment for the various covariates, we presented the results

as a stepwise analysis with groups of independent variables, as shown in Table 2 in paper III.

Bonferroni correction is a well-known tool for adjusting for multiple testing in clinical trials, however, less often used in observational cohort studies. The criticism against this correction is that it gives a very conservative estimate with the risk of rejecting true associations (Type II errors). In our studies, Bonferroni corrections were not applied because the risk of Type II errors was considered greater than the risk of accepting false associations (Type I errors)

3.5 Ethical considerations

The Regional Committee for Medical Research Ethics in Western Norway approved the study and research protocol (REK 2010/788). The studies were performed after the end of MoBa inclusion, and therefore had no effect on questionnaire formulation or data collection. Informed consent was obtained from each MoBa participant upon recruitment, and data were recorded anonymously. Participation in MoBa was voluntary with the opportunity to withdraw from the study at any time. It is important to consider the benefits vs. possible inconvenience for the participants from both the practical participation and from the results. Revealing associations between epilepsy and adverse socioeconomic conditions and mental health complaints can be stigmatizing for young women and men with epilepsy. Knowledge about these conditions can on the other hand without doubt reinforce preventive measures and improve treatment.

4. Results

4.1 Paper I

Among women included in the study, 0.7% (n = 711) reported a history of epilepsy, and 45.9% of these were treated with AEDs. In the AED group the majority used monotherapy (81.5%). Only 0.036% (n = 39) used AEDs for reasons other than epilepsy. Excluding such pregnancies from the control group without epilepsy had a minimal effect on the risk estimates in the group with epilepsy.

A diagnosis of current or previous psychiatric disease was reported by 10.1 % (n = 10,810) of all women in the study, with a significantly higher frequency in the epilepsy group (13.4 %, OR = 1.4, CI = 1.1–1.7, p = 0.004), and also in the epilepsy subgroup with no AED treatment (16.2 %, OR = 1.7, CI = 1.3–2.3, p < 0.001). The AED polytherapy subgroup had the highest report of psychiatric comorbidity when compared with the references, but numbers did not reach significance (16.7 %, OR = 1.8, CI = 0.90–3.5, p = 0.091). Both prior to and during pregnancy, depression was the most common self-reported psychiatric diagnosis in the study cohort, with a significantly higher frequency in women with epilepsy prior to pregnancy compared to the references (9.0 % vs. 6.2 %, OR = 1.5, CI = 1.2-1.9, p = 0.002) (paper I, Table 4). The difference was also significant for the AED-untreated subgroup (9.9 % vs. 6.2 %, OR = 1.7, CI = 1.2-2.3, p = 0.003), but not after adjustment for confounders in a regression analysis (paper I, Table 4). Self-reported depression was most frequent in the AED polytherapy group both before and during pregnancy, though not statistically significant when compared with the references (11.7 %, p = 0.099, and 5.0 %, p= 0.18, respectively). Anxiety was reported more often by the AED-untreated women compared to the references prior to pregnancy (5.5 % vs. 3.4 %, OR = 1.7, CI = 1.1-2.6, p = 0.023). This association was not consistent after logistic regression. Eating disorders were more common in epilepsy compared to the references before pregnancy (4.8 % vs. 2.9 %, OR = 1.7, CI = 1.2-2.4, p = 0.003), and even higher in the AED-untreated subgroup (6.8 % vs. 2.9 %, OR = 2.4, CI = 1.6-3.6, p < 0.001). The

association remained significant for the AED-untreated subgroup after adjustment for potential confounders (OR = 1.9, CI = 1.3–2.9, p = 0.002).

Symptom scores for present depression (SCL) (in paper I named HSCL) were increased in epilepsy (paper I, Table 5), in both AED-treated and untreated women with epilepsy. The scores were significantly higher for the polytherapy and LTG subgroups compared with the controls, and consistent for AED-treated women after logistic regression (OR = 1.5, CI = 1.1–2.1, p = 0.009). LTMD scores for previous depression were increased in AED-treated women, with the highest scores for the polytherapy group (paper I, Table 5), and significant after adjustment for confounders (OR = 1.5, CI = 1.0–2.2, p = 0.045).

Educational level ≤ 12 years was more common in both AED-treated and untreated epilepsy (paper I, Table 2), including the polytherapy and the three monotherapy groups (paper I, Table 3). Low income was more frequent in the AED group (paper I, Table 2 and 3), and so were reports of "no income", especially for the LTG-treated group (7.1 %, OR = 2.9, CI = 1.3–6.2, p = 0.014). Likewise unemployment due to disability was associated with epilepsy, particularly for the group with AED-treatment, with 23.3 % unemployment in the AED polytherapy group. Single parenting was more common in both AED-treated and untreated women, also in the polytherapy (8.3 %, OR = 3.8, CI = 1.5–9.4, p = 0.01) and LTG groups (7.0 %, OR = 3.1, CI = 1.4–6.7, p = 0.010). Smoking was more common in the AED-treated women than in the references, whereas alcohol consumption during pregnancy and use of narcotics before pregnancy was similar in women with and without epilepsy compared with the references. Repeated pregnancies in the same women had minimal effect on risk estimates (paper I, supplementary material).

4.2 Paper II

Among the men included in the MoBa study, 0.9 % (n = 658) was registered with a diagnosis of epilepsy (paper II, Table 1). During the last six months prior to their

partner's pregnancy, 36.9 % (n = 243) of them reported having used AEDs, of which 87.2 % (n = 212) used AEDs as monotherapy.

Symptoms of anxiety (SCL-A) and depression (SCL-D) during partner's pregnancy were more common in men with epilepsy than the references without epilepsy, but not more common compared to men with NNCD (paper II, Fig 1). The association between epilepsy and anxiety was consistent after adjustment for confounders (paper II, supplementary S2 Table), but not for depression. Previous depression was the most common screening positive diagnosis (LTMD) among all men in MoBa, and significantly increased in AED-treated men with epilepsy compared to the references (15.0 % vs. 10.0 %, OR = 1.6, CI = 1.1-2.2, p = 0.012) (paper II, Fig 1). Men with a history of depression more often reported current anxiety (21.8% vs. 2.7%, OR = 10.2, CI = 9.5–10.9, p < 0.001) or depression (13.7% vs. 1.3%, OR = 12.6, CI = 11.5–13.8, p < 0.001) during pregnancy compared to those without previous depression, with no significant difference between the epilepsy and the non-epilepsy group. Frequency of anxiety or depression did not differ in men who reported expecting their first child vs. those with previous children. ADHD was the second most common screening-positive diagnosis in all the expecting fathers (paper II, Fig 1 and supplementary S2 Table), without any significant difference between the epilepsy group and the two reference groups. Screening-positive ADHD showed a higher prevalence than self-reported ADHD in men both with and without epilepsy (paper II, Fig 2). In the epilepsy group 2.2% were registered with a self-reported ADHD-diagnosis, while 9.5% had a positive symptom score for ADHD (p < 0.001).

A self-reported psychiatric diagnosis was more often registered in men with epilepsy compared to the reference group (6.9% vs. 3.1%, p < 0.001), but not compared to the NNCD group (6.9% vs. 4.5%, p = 0.076). The self-reported psychiatric diagnoses were mainly associated with AED-untreated epilepsy (paper II, Fig 3). Both self-reported ADHD (2.2 % vs. 0.4 %, OR = 5.2, CI = 2.3-11.8, p = 0.002) and bipolar disorders (1.8 % vs. 0.3 %, OR = 5.6, CI = 2.3-13.9, p = 0.003) were increased in expecting fathers with epilepsy compared to both reference groups. After adjustment for confounders, the differences remained significant between the epilepsy and the main

reference group (paper II, supplementary S3 Table). Other unspecified psychiatric disorders were also more common among fathers with epilepsy compared to the healthy references (4.3 % vs. 2.3 %, OR = 2.0, CI = 1.1-3.5, p = 0.022) and consistent after adjustment for confounders (paper II, S3 Table).

Psychiatric diagnoses and symptoms were assessed in subgroups according to type of AED-treatment; polytherapy and three monotherapy groups. The majority of observations were so rare that significant differences should not be expected (paper II, supplementary S4 Table).

Low self-esteem (2.5 % vs. 1.3 %, OR = 1.9, CI = 1.2-3.1, p = 0.011) and low satisfaction with life (1.7 % vs. 0.7 %, OR = 2.3, CI = 1.3-4.3, p = 0.010) were more common in men with epilepsy compared to the references without epilepsy and compared to NNCD (paper II, Table 2), and this association between epilepsy and low satisfaction with life remained significant after adjustment for confounders (paper II, Table 2).

Low income, unemployment due to disability, and financial problems were more common in epilepsy compared to the references without epilepsy, and more common than in NNCD patients (paper II, Table 1). The proportion of men with epilepsy reporting sick leave for more than 8 weeks yearly was higher than in men with than without epilepsy (11.2 % vs. 6.2 %, OR = 1.9, CI = 1.2-3.0, p = 0.005) and in the NNCD group. Several well-defined adverse life events experienced during the past 12 months were also more common among fathers with epilepsy compared to the reference group without epilepsy and the NNCD group, for instance financial problems (25.2 % vs. 15.1 %, OR = 1.9, CI = 1.4-2.5, p < 0.001), interpersonal conflicts (24.9 % vs. 16.7 %, OR = 1.7, CI = 1.3-2.2, p < 0.001), severe injuries or illness (11.0 % vs. 4.3 %, OR = 2.7, CI = 1.8-3.9, p < 0.001) or episodes of violence (3.6 % vs. 1.5 %, OR = 2.5, CI = 1.3-4.8, p = 0.008) (paper II, Table 3).

4.3 Paper III

Mean scores for life satisfaction and self-esteem were lower in the women with epilepsy compared to those without epilepsy at all three survey times; at pregnancy weeks 13-17, and 6 and 18 months postpartum (paper III, Table 1). At pregnancy weeks 15-19 the epilepsy group had higher mean scores on work strain, and 18 months postpartum they reported lower levels of general self-efficacy and quality of somatic health. The association between epilepsy and life satisfaction remained significant with a negative correlation after linear regression for various aspects (paper III, Table 2).

Distinct unfavourable scores for low self-esteem was more common in women with epilepsy compared to the references both during pregnancy (6.6 % vs. 3.5 %, OR = 2.0, CI = 1.4-2.7, p <0.001=), and at 6 months (6.8 % vs. 3.7 %, OR = 1.9, CI = 1.4-2.7, p <0.001) and 18 months postpartum (7.5 % vs. 4.3 %, OR = 1.8, CI = 1.2-2.6, p = 0.002) (paper III, Figure 2A-C and supportive Table S2). During pregnancy low maternal relationship satisfaction was associated with epilepsy (7.9 % vs 5.1 %, OR = 1.4, CI = 1.0-1.9, p = 0.033), while at 18 months postpartum mothers with epilepsy were more likely to report low global life satisfaction (10.9 % vs. 6.0 %, OR = 1.9, CI = 1.4-2.6, p < 0.001), low quality of somatic health (20.3 % vs. 13.4 %, OR = 1.6, CI = 1.3-2.2, p = 0.002,) and low general self-efficacy (8.2 % vs. 3.7 %, OR = 2.3, CI = 1.6-3.3, p < 0.001) compared to mothers without epilepsy. After regression analysis the association between epilepsy and low self-esteem remained significant at all three time points, and so did the correlation for low global life satisfaction, low quality of somatic health and low general self-efficacy (paper III, supportive Table S2).

Single parenting showed a negative correlation with life satisfaction at all three time points, (paper III, Table 3). Smoking, low income, low educational level and sick leave also correlated negatively with life satisfaction at pregnancy weeks 13-17, and so did lack of financial security and adverse life events 6 months postpartum. At 18 months postpartum only, there was a significant and negative correlation between AED use and life satisfaction. Low self-esteem, low relationship satisfaction, emotional distress, low social support, high work strain, low general self-efficacy and low quality of

somatic health all correlated negatively with life satisfaction in women with epilepsy at all three time points (paper III, supportive Table S4).

Women with epilepsy more often reported rare contact with other persons than their partner at pregnancy weeks 15-19 compared to the references (1.9 % vs. 1.0 %, OR = 1.8.CI = 1.1-3.2, p = 0.028), and more often experienced feelings of loneliness 18 months postpartum (4.2 % vs. 2.3 %, OR = 1.8, CI = 1.1-3.0, p = 0.013) (Paper III, Figure 2).

Pregnant women with epilepsy were less often in a relationship compared to the references (94.1 % vs. 96.6 %, OR = 0.56, CI = 0.41-0.77, p <0.001) (paper III, Table 5), and more likely to have unplanned pregnancies (23.9 % vs. 19.5 %, OR = 1.3, CI = 1.1-1.6, p = 0.007) and to report sick leave during pregnancy (36.8 % vs. 28.6 %, OR = 1.5, CI = 1.2-1.7, p < 0.001). Lack of financial security was associated with epilepsy at both 6 months (23.4 % vs. 16.6 %, OR = 1.5, CI = 1.2.2.0, p = 0.003) and 18 months postpartum (9.5% vs. 6.8 %, OR = 1.5, CI = 1.0-2.9, p = 0.028). Not living with the child's father (7.2 % vs. 4.2 %, OR = 1.8, CI = 1.2-2.6, p = 0.002) and unemployment (27.5 % vs. 19.9 %, OR =1.5, CI = 1.2-1.9, p < 0.001) were more common in women with epilepsy 18 months postpartum (paper III, Table 5).

Adverse life events reported 6 and 18 months postpartum were more common in mothers with epilepsy, including financial problems, separation/divorce, interpersonal conflicts, worries about the child, having been seriously ill or injured, and having been involved in accidents/house fire/robbery (paper III, Table 6).

5. Discussion

5.1 Methodological considerations

5.1.1 Population based design

The foundation of this work is data from non-experimental, observational studies and registries (170). We used longitudinal data from a national population based prospective health study, MoBa (145), and additional data from a national health registry, MBRN (149, 150). All three studies included in this thesis were cross sectional. Being population based, our study cohort covers participants from all over the country and from all socioeconomic groups. Cohort studies may be susceptible to selection and observational bias, and loss to follow up is a challenge in prospective designs (171). They are also less appropriate for establishing causative relationships than case control studies (172). Population based cohort studies are, however, powerful tools for studying differences and associations in large populations and over time (171). The strongest advantage of this design is the large number of participants, enhancing power in statistical analysis. A second strength is generalizability. Information from unselected participants from the general population is more generalizable than information from hospitalized or institutionalized patients. The demographic information often available in cohort studies makes comparison between groups possible, i.e. by adjusting for age, gender and socioeconomic aspects. Ethical aspects and costs are challenges not only in basic science and clinical trials, but also in epidemiological research (170, 173). The quantitative design with self-reported data through questionnaires is, however the easiest and most cost-effective way to assess such a wide spectrum of information on both demographic, social, health, and life style matters from so many participants. It is also possible to study several outcomes at the same time.

The study cohort in our work consisted of a national sample of pregnant women and their partners. Epilepsy was the main exposure of interest and psychiatric comorbidity, life quality and socioeconomic aspects were the main outcomes. The recruitment from the general population included both AED-treated and untreated persons with epilepsy,

thereby avoiding overestimation of disease severity typically associated with institutional-based studies. A heterogeneous reference group, not only including healthy controls, reduced the chance of overestimating risks in the target group. As mentioned earlier, the cohort design also facilitated comparison between several groups, such as a second control group of persons with NNCD.

Important epidemiological questions about health in a population or community that can be answered through cohort studies are "What are the health problems and the prevalence of these in the community?", "Where do they occur?", "Who are at risk?", and "What are the risk factors for such health problems?". Upon identifying prevalence and cause of disease health authorities can initiate surveillance and screening programs, provide preventive measures and optimal treatment, and evaluate therapies (172).

5.1.2 Internal validity

Internal validity reflects the accuracy of observations within our study population (170), i.e. that the observed associations are truly caused by the variables studied (172). Upholding of internal validity requires appropriate definition and measurement of exposure and outcome as well as proper statistical approaches for identifying associations between them (174). Internal validity can be influenced by systematic errors. Particularly important among the latter are selection bias, information bias, and confounding (170).

Selection bias

Selection bias is caused by factors determining subject inclusion and study participation (174) and may occur at inclusion, or during the follow-up period of the study. For instance, study design may limit inclusion, and demographic and

socioeconomic characteristics may affect participation. The exposure-outcome association will then differ for those participating in the study and those who do not.

MoBa may be vulnerable to selection bias at several levels of conduction. The MoBa cohort is by definition subject to a degree of selection bias as it only includes pregnant women and their partners. Pregnant couples, generally tend to be healthier and have a more stable socioeconomic background compared to those who do not become pregnant and/or establish a family (174). Another selection factor was the ability to read Norwegian, as the study information and questionnaires were only available in this language (146), therefore excluding a substantial part of certain ethnic minorities from the study population. Geographically, the whole country was sufficiently covered, as participants were recruited from 50 out of a total of 52 hospitals with maternity units in Norway (147). Notably, selection bias occurring at baseline may overlap with the concept of confounding (170).

Selection bias may also result from incomplete population participation in the study. The overall participation rate in MoBa was 41 % out of 277,702 invited women (146). The populations of voluntary participation studies have been shown to differ from those of compulsory registries (172). This introduces self-selection (170), which may influence internal validity, as the motive for participating may be associated with the outcome under study. The questionnaires in MoBa are detailed and thorough, and take time and patience to fulfil. This can lead to an overrepresentation of more resourceful participants, who tend to have better health and socioeconomic status, therefore influencing study outcomes (175, 176). However, inclusion in pregnancy weeks 13-17, before the scheduled routine ultrasound in pregnancy weeks 18-19, implied that participation was accepted irrespective of the ultrasound result and potential pregnancy outcome (145). As selection bias is a well-known challenge in epidemiological surveys, a validation study of prevalence and risk estimates in MoBa was carried out by Nilsen *et al.* (177). The authors compared estimates in MoBa with the national compulsory MBRN, the latter including all pregnant women during the MoBa-inclusion period. Their results indicated that several prevalence estimates differed between the cohort participants and the total population of pregnant women. Women

in MoBa had a higher mean age, they were less often smokers and more often in a relationship. However, epilepsy prevalence did not differ between the two populations and was found to be within the expected range of the general population. In addition, measures of exposure-outcome associations, i.e. risk estimates, were not affected by bias. This was further corroborated by a validation study of the Danish National Birth Cohort, which is very similar in overall design, showing that exposure-outcome estimates were unaffected by bias (175). Therefore, although self-selection may skew our study cohort towards more favourable outcomes, comparison between subgroups in the cohort remains valid.

Yet another potential source of selection bias is the dropout rate in MoBa of about 36 % from the first questionnaire during pregnancy and until 18 months postpartum (paper III). There is a risk that the persons lost to follow-up are those with most socioeconomic challenges and greatest disease burden (172). Mothers who experience birth complications or mothers of children with severe illnesses or developmental delay might be either over- or underrepresented during follow-up. Overrepresentation may be due to a special interest in study outcome for their child, while time-consuming treatment and adjusted care of a chronically ill child can lead to drop out. The latter was indicated in a previous study from MoBa, showing that mothers of children with severe developmental delay had lower response-rate to the postpartum follow-up questionnaires (178). Notably, the prevalence of epilepsy remained stable between 0.6-0.7 % during the study period, so the percentage lost to follow-up was approximately the same in the study and reference group. Also, in a previous study on mothers with epilepsy in MoBa, analysis on a subgroup of AED-treated mothers showed that maternal demographic data did not differ between mothers lost to follow-up at 18 and 36 months postpartum and those still participating at these time points (179). Because the dropouts could potentially affect the assessment of outcomes and scores between groups at different time points, we chose to focus on comparisons between the epilepsy and reference group at each survey time.

The second source of data in this work is MBRN (150). This cohort is highly representative for the national population of pregnant women in Norway due to

compulsory registration of information. The recording of information is performed by health personnel, either the general practitioner or a midwife, and starts from the first prenatal care visit, with several follow-up appointments during pregnancy, and finally at delivery. This has two major advantages: Firstly, it rules out selection bias, and secondly, by registering some of the information during birth, recall bias (see information bias below) is reduced

Information bias

Information bias can be caused by error in assessment of both exposure and outcome variables in a study (174). Information bias concerning categorical variables is also termed misclassification, which is subdivided according to the characteristics of the variables (170). Misclassification of a variable that depends on the values of other variables is called differential misclassification, whereas misclassification of a variable that is independent of the value of other variables is called non-differential misclassification.

One important type of differential misclassification of concern in this work is recall bias (174). Some of the information in MoBa is vulnerable to recall bias because the participants are asked to remember in detail daily routines and happenings that occurred weeks or months ago. Adverse events can result in participants recalling true exposures differently than those who did not experience the adverse events (170). This can cause either an over- or underestimation of exposures. For instance, mothers of babies with malformations may be more likely to recall various exposures during pregnancy than mothers of healthy babies. Information on the epilepsy diagnosis reported by the participants may also be biased due to either erroneous recollection or uncertainty about the diagnosis. Severe epilepsy with AED-dependency is more likely to be reported than inactive epilepsy, which may cause some participants to be misclassified as “unexposed”. Because of the large number of references in our study cohort, such a misclassification will likely not affect this group, but could skew the epilepsy group towards more adverse outcomes.

Even though a variable originally may have the characteristic of being independent of other variables, the construction of new variables from one or more original variables opens up to differential misclassification (170). Many of the variables used in all three papers of this work, for instance the screening tools, are based on other original variables. In order to minimize the relatively unpredictable effect of differential misclassification, and to be able to correct potential errors and make data reproducible, construction of variables was documented by using syntaxes in SPSS. The syntaxes were also sent to a special steering committee of MoBa, enabling other researchers to use and refine the same scripts.

Missing data was a challenge when using screening tools based on scales. Cut-off values were either predefined based on recommendations in the literature, or defined relative to mean values. Missing values could therefore either shift the proportion estimated to have a positive or negative symptom score, or even make it impossible to use the screening tools. In order to account for missing data, the missing value was replaced with the mean of the observed value for data, mean imputation (180), calculated by the statistical program SPSS. Imputation was applied only if less than 20 % of data were missing on the scales. Another alternative would have been to discard all scale-data with missing values. This would, however, render the data more vulnerable to random errors due to reduced sample size (180). Using imputation is therefore an acceptable compromise in order to exploit the available data.

Non-differential misclassification due to erroneous registration of either exposure or outcome in databases as large as MoBa and MBRN is unavoidable. Renewal and revision of MoBa-questionnaire versions introduces bias because it affects registration and interpretation of data (147). In this work, the effect of revision of questionnaires complicated comparisons of outcomes between the three survey points in paper III, contributing to the decision of avoiding such comparisons. Moreover, deliberate misreport of sensitive data by the participants may also introduce non-differential misclassification. Adverse psychosocial conditions, such as alcohol or substance use and depression, may be underreported. The discrepancy between self-reported and screening positive psychiatric diagnoses found in our population could indicate such

kind of information bias. The anonymous design of questionnaires should decrease this type of error. The participants are not confronted by an interviewer and may therefore feel more comfortable in reporting sincere answers. Nevertheless, lack of trust in anonymity makes participants more inclined to withhold or alter personal information to conform with social norms (181). Expecting parents in our study may feel particularly vulnerable, as their answers in the MoBa questionnaires concern not only themselves, but also their children.

MoBa and MBRN were not designed specifically to evaluate epilepsy or epilepsy-outcomes, and the lack of clinical information in MoBa is a limitation. By record linkage of the two databases, the validity of diagnoses and medication, as well as other information such as smoking, were strengthened. As mentioned earlier, diagnostic information in MBRN is considered highly reliable. Record linkage is important to minimize the challenge of missing data, as described previously (172). In the first validation study of MoBa by Nilsen *et al.*, the prevalence of epilepsy was comparable to that in the compulsory MBRN (177), and was in both registries near the expected estimate of 0.7 % for the general population. Several thorough studies support this initial evaluation. In a recent validation study of women with epilepsy in MoBa, hospital records confirmed the epilepsy diagnosis in 95 % of the cases, and information on AED-treatment was confirmed for 100 % (179). In another retrospective validation study of the epilepsy diagnosis in MoBa, 300 questionnaires were completed by women with epilepsy from MoBa and confirmed the initial reported diagnosis for 98 % (166). Further details on epilepsy type and seizures were also obtained. 86 % reported unchanged disease severity during pregnancy, whereas 9 % reported worsening. The high validity of AED-use in women with epilepsy in MoBa has also been demonstrated through a 95 % correlation between plasma samples and reported AED-use (166, 168). The epilepsy diagnoses in MBRN have shown a high degree of reliability. Validation of disease registration in MBRN has previously been performed through record linkage of MBRN with another population-based registry, the Norwegian Prescription Database (182). The results showed an estimated sensitivity of 74 % for epilepsy in MBRN, and a specificity close to 100 %. A large part of AEDs were dispensed to pregnant women without a diagnosis of epilepsy,

which probably explains the low sensitivity. Results from a validations study comparing 222 hospital records of mothers registered with an MBRN-epilepsy diagnose verified 93 % of the diagnoses (183). The overall conclusions from these studies are that the validity of epilepsy-related information in both MoBa and MBRN is very good and probably more representative for the general population than clinical-based cohorts.

The psychiatric diagnoses obtained from single questions in MoBa, such as depression and anxiety in women, and ADHD and bipolar disorder in men have not been validated, which represents a limitation of our studies. Due to lack of similar information in MBRN the prevalence of the diagnoses were not possible to validate through the registry linkage. Several of the psychiatric diagnoses assessed from symptom score are, however, based on well-known and validated screening tools, such as present symptoms of depression and anxiety (SCL), previous depression (life time major depression, (LTMD), and ADHD (ASRS), as described in the Material and Methods section. Both the screening tools for psychiatric symptoms and the scales for different aspects of life satisfaction have been used in several publications from MoBa (184-187). Although anonymity is assured, participants may be reluctant in sharing sensitive information about mental health, and shame and stigma associated with mental health issues may lead to an underestimation of such aspects (181). The comparison of information on self-reported psychiatric diagnoses and symptoms score in our work indicates such underreporting. Questions about symptoms may be less easy to recognize as part of screening tools, or they may feel less vulnerable to report than a definite diagnose.

In both paper I and II we used LTMD to estimate depression previous to pregnancy. In the LTMD scale the question is expressed as follows “Have you ever experienced the following for a continuous period of 2 weeks or more?” Since the question was answered in pregnancy weeks 13-17, we could have measured a combination of depression in an early stage of pregnancy and depression previous to pregnancy. Interpretation of pre-pregnancy depression assessed through symptom score must therefore be done with caution.

The variable use of Hopkins symptoms check list (SCL) in the questionnaires complicated the use of the scale. In MoBa-questionnaire 1 the scale was used with five items, whereas in later versions eight items were included. To be sure that we operated with the same five items for SCL in regression analysis in paper III, we had to exclude three items at 6 and 18 months postpartum. This may have affected the association for SCL whenever the instrument was included in an analysis.

Confounding

A confounder is an extraneous factor that correlates with both the dependent and independent variables, causing an erroneous conclusion about their apparent association (170, 174). There are three criteria for defining a confounder: 1) It should be a risk factor for the outcome, 2) It should be associated with the exposure of interest in the study population, 3) It should not be an intermediate in a causal way between exposure and outcome (172, 174). Confounding was considered in all three papers of this thesis, and crude results were further analysed to adjust for potential confounders. Classical confounders selected *a priori* included age, low income and low educational level in paper I-III. In addition, adverse socioeconomic variables that differed significantly between the epilepsy and reference groups were considered as possible confounders when relevant. In paper I this included unemployment due to disability, single parenting, and smoking. In paper II unemployment due to disability and sick leave were included. In paper III, we also included social support and adverse life events, however stepwise, in some of the adjusted analyses. While failing to identify confounders may cause spurious associations, over-adjustment may weaken, or even remove, a true association between the dependent and independent variables. In paper I-III, the unadjusted and adjusted risk estimates were, however, generally quite similar. This may be due to a stronger relation between the main exposure and outcome, than between the potential confounder and exposure or outcome.

5.1.3 External validity

External validity is an extension of internal validity and refers to the applicability of the results from a study population to the general population, i.e. generalizability (174). In order to get a representative study population, cohort studies can be designed to include only subjects with a specific property characteristic of the target population (170). MoBa was designed to include pregnant women, their partners, and later their children. The limitation from this kind of design is that generalisations cannot be made beyond the target population, or at least one should do this very cautiously. The aim in this work was to investigate pregnant women and their partners, so the study design was not a limitation concerning pregnancy and should be representative for the general population of pregnant persons in Norway. For the epilepsy group specifically, the numbers registered with AED treatment was quite modest, both in women and men. AED treatment is associated with more severe epilepsy, and it is likely that those who get pregnant are healthier and more often have inactive epilepsy. Another plausible explanation is that pregnancy is planned in an optimal phase of life, when the condition is well regulated. It is possible that the women and men with epilepsy in our cohort are slightly healthier and struggles with less socioeconomic challenges than the general population of persons with epilepsy (177).

5.1.4 Random errors

Random errors may be introduced during data collection, registration or analysis. Random errors reduce the precision of the risk estimate, which is expressed through the CI. A wide CI demonstrates a large degree of random errors (low precision), whereas a narrow CI demonstrates a small degree of random errors (high precision) (172). In contrast to systematic errors, increasing the study population size diminishes the effect of random errors. Both the target and the reference groups in this work are sufficiently large to minimize random errors, and outcomes are relatively common, as seen from the narrow CI of outcomes. However, even in our cohort investigation of risks related to some of the AED subgroups were challenged by few observations.

Continuous work with correction of information and coding errors in MoBa has improved data quality further and decreases random errors in updated versions (147).

5.2 Interpretation of results

5.2.1 Epilepsy and AED-treatment

The prevalence of epilepsy found in all three papers was within the expected range for both women and men (31, 32). Pregnancy itself could explain the relatively low proportion of AED-treated women, as many may choose not to use medications during pregnancy. Although newer studies suggest that AED-treatment is safe during pregnancy and breastfeeding (139), inclusion in the MoBa study was conducted in a time period when there was much debate around AED-use in pregnancy (136, 188, 189). This is, however, not the reason for the low percentage of AED-medicated men with epilepsy. A more probable explanation is that both men and women were in an optimal phase for family planning, i.e. they had a period with inactive epilepsy, free of epileptic seizures and/or AED-treatment. The formulation of the epilepsy-question in our material opens up for inclusion of persons who have been seizure free since early youth or maybe even since childhood. This is another plausible explanation for the low percentage of AED treated epilepsy in both genders, which is corroborated by the results of another recent study on women with epilepsy in MoBa (166).

5.2.2 Socioeconomic conditions and adverse life events

Lower educational level, low income, sick leave and unemployment due to disability are some of the conditions that were more pronounced in persons with epilepsy during and after pregnancy. In addition, maternal epilepsy was linked to single parenting. These social aspects are all strong predictors of mental health and quality of life (190). Living with a chronic disorder in general may partly account for some of the above-mentioned adverse aspects. Several conditions were, however, also more common in

expecting fathers with epilepsy when comparing them to men with NNCD. In a previous study, we found the same pattern for women with epilepsy compared to women with NNCD in MoBa (168). This suggests that epilepsy for important health aspects implies a greater burden than other chronic disorders. Early onset of epilepsy may affect school achievements, educational possibilities, and social relationships (81-83), which can extend into adult life with negative influence on work opportunities and the chance of finding a life partner (92, 93). Being single or unmarried is also previously found to be more common in persons with epilepsy in non-pregnant populations (92, 93), which is unfortunate, as single status and poor social support is shown to be particularly unfavourable for emotional distress in epilepsy (191, 192). Optimal seizure control is associated with a favourable employment history (193). In Norway, women are expected to work until three weeks before delivery, in other countries this working period may even be longer. Pregnancy complications *per se* may challenge the work situation, in which case coping with potential seizures and AED treatment would be an extra burden. The degree of decreased social integration seen in persons with epilepsy depends for a large part on the severity of the condition (91, 194), with AED polytherapy as an important indicator of severity. When we examined polytherapy in pregnant women with epilepsy, we did find many adverse aspects to be most pronounced in this subgroup. While this effect may be partly ascribed to the epilepsy itself, it is plausible that side effects due to a greater drug load play a role. Although several associations were not significant, the overall results for the polytherapy group probably reflect a more complicated epileptic disorder with higher seizure frequency, particularly in pregnant women with epilepsy, where even the justification of AED used as monotherapy has been debated for years (136, 188, 189).

Unemployment is a socioeconomic burden, and in our material a large part of both expecting men and postpartum women with epilepsy reported inability to handle unexpected expenses or having experienced economic problems during the last 12 months. Financial stability is important for mental well-being and feeling of security for the family (195), especially during and after pregnancy. Having a job provides financial security, both through direct income, and also by securing financial support

for the period of parental leave in the last part of pregnancy and postpartum. In addition, a job usually provides a social network and psychological support, also vital in the situation as new parents. Having a baby implies strains on both economical and time budgets. A recent study showed that even though becoming a parent is mostly associated with positive feelings, couples experience a decline in relationship satisfaction due to family expansion (196). Struggling with practical issues such as unemployment, financial insecurity and job application may push relationship closer to a break up. In Scandinavian countries, the population benefits from a highly developed social welfare system, with financial support during parental leave, in situations of unemployment, under conditions with chronic illnesses, as well as in relation to drug expenses for chronic illness. Despite of this and even in a study population where previous research suggests that the participants are quite resourceful (177), pregnant women and men with epilepsy tended to have a worse outcome than women and men without epilepsy.

Our results also suggested that expecting fathers with epilepsy, and postpartum mothers with epilepsy, were prone to experience more adverse events, such as conflicts with other persons, serious accidents, illnesses, and worries about their children. Accidents and illnesses could be caused by epileptic seizures, or perhaps in part be related to side effects from AEDs (197). The mothers with epilepsy more often reported worries about their children, which may also be related to their epilepsy. For instance, worry about development in the child when having been exposed to AED during pregnancy, or anxiety for having a seizure when left alone in care of the child (198). Proper information and counselling of mothers with epilepsy is important as it reduces worries and prevents epilepsy-related accidents (122, 199). Other adverse events associated with epilepsy were interpersonal conflicts in both genders and episodes of violence in expecting fathers. Behavioural issues have been associated with epilepsy, but mainly linked to severe epilepsy with comorbidity, in association with syndromes, or in relation to specific antiepileptic treatment (200, 201). A previous study demonstrated that youths and adolescent men with epilepsy exhibited risk-taking behaviour more often than their peers without epilepsy, including criminal offences (88). The question in the expecting fathers' MoBa-questionnaire did not

specify how the men were involved in such episodes, so it is unknown whether they initiated the episodes through provoking behaviour, or whether they were exposed to physical assaults by other persons.

5.2.3 Psychiatric diagnoses and symptoms

The epilepsy groups differed significantly from their references regarding several psychiatric disorders and psychological complaints. The low proportion treated with AEDs could, as mentioned earlier, indicate inactive or less severe epilepsy. This may partly explain the moderate frequency of psychiatric comorbidity associated with epilepsy in our studies compared to many previous reports on persons with epilepsy (67, 71, 78). Methodological differences from other studies must also be considered as a reason for the lower prevalence of psychiatric complaints. Recruitment from the general population of expecting women and men should reflect a more accurate prevalence of psychiatric comorbidity than cohorts based on clinical studies with institutionalised populations.

As expected from previous studies on non-pregnant persons with epilepsy (202), depression and depressive symptoms were the overall most common psychiatric complaints. Depression, assessed as a self-reported diagnosis, was more pronounced in women with epilepsy prior to pregnancy compared to the references without epilepsy, but not when assessed as symptom score for previous major depression (LTMD). The discrepancy between the self-reported depression diagnosis and the symptom score-diagnosis could reflect that women with epilepsy did in fact more often experience depression prior to pregnancy, but not with symptoms as severe as for LTMD. The opposite was true for depression during pregnancy, where a self-reported diagnosis did not differ between the epilepsy and reference groups, whereas present depression assessed through symptom score (SCL) was significantly higher in women with than without epilepsy. There was a clear discrepancy in prevalence between a self-reported diagnosis of depression and assessment through symptom score during pregnancy for all the women in the cohort. Observations in the epilepsy group showed that 2.7 %

reported a diagnosis of present depression, whereas 16.4 % had a positive symptom score for present depression. This could indicate that depressive symptoms are underreported in pregnancy. Alternatively, the specificity of SCL may be too low, thereby overestimating the symptom score. However, probable underreport of or unrecognized depression as an explanation is supported by our earlier work on the same population, where we found that pregnant women with epilepsy and comorbid depression were less likely to receive antidepressants than women without epilepsy (168). Nor does the relatively low prevalence of depression in our study population compared to other studies on pregnant women or persons with epilepsy suggest an overestimation of symptom score (71, 130). Importantly, the overall highest frequency report on depression in paper I was for scores of current depression measured by SCL during pregnancy, in both women with and without epilepsy (paper I, Table 4 and 5). Pregnancy follow-up should account for such vulnerability, and particularly in women with epilepsy.

For expecting fathers with epilepsy (paper II), previous major depression assessed through symptom score (LTMD) revealed an isolated higher frequency in those with AED-treatment compared to references without epilepsy. Screening positive present depression (SCL-D) and anxiety (SCL-A) were also more pronounced in the expecting fathers with epilepsy compared to those without epilepsy. Prenatal depression is previously shown to be a predictor of postnatal depression in both genders (168, 203, 204). Importantly, parental peripartum depression is associated with developmental delay and emotional distress in their children (205, 206). As there was no difference in prevalence for depression or anxiety when comparing fathers with epilepsy with the NNCD group in paper II, the association between epilepsy and depression and anxiety may reflect the burden of a chronic disorder rather than an epilepsy-specific effect. The adjustment for various adverse socioeconomic aspects weakened some of the associations between epilepsy and mood disorders. This implies that the influence of epilepsy on everyday life, social functioning and quality of life is probably also important in explaining depression and anxiety in the expecting fathers, in addition to epilepsy *per se*. For the expecting mothers with epilepsy we did not find a difference in a self-reported diagnosis of anxiety compared to those without epilepsy. This is in

contrast to previous studies on non-pregnant persons with epilepsy (207), and in contrast to a case-control study, where women with epilepsy reported a significantly higher rate of birth anxiety than women without epilepsy (208). However, during women's pregnancy (paper I) we did not specifically examine birth anxiety, but rather a more general diagnosis of anxiety, which could be expected to be less common in healthy pregnant women as opposed to birth anxiety (209, 210). The formulation of the MoBa question on anxiety and the prevalence estimate of anxiety reflect that we most likely recorded general anxiety and not birth anxiety (Appendix I).

Bipolar disorder was the only specific affective disorder registered as a self-reported diagnosis in the fathers' questionnaire, and we found that it was more common in expecting fathers with than without epilepsy, and more common compared to men with NNCD. This is in line with previous studies on epilepsy and bipolar disorder in non-pregnant persons (211). The stronger association with epilepsy than with NNCD indicates an epilepsy-specific effect. A common aetiology has previously been proposed for these two conditions, supported by clinical observations that they both respond to the same drug treatment (212, 213). Further, bipolar disorder is a risk factor for onset of epilepsy, and bipolar disorder occurs more often in person with than without epilepsy (76, 214).

A self-reported diagnosis of ADHD was more common in fathers with epilepsy compared to both the overall reference group and to men with NNCD. Independent of pregnancy status, ADHD has previously been reported to be associated with epilepsy (215). It may be that early onset of epilepsy in childhood or adolescence increases the possibility of identifying ADHD in persons with epilepsy due to extra clinical follow up. Another plausible explanation for this increased co-occurrence could be that epilepsy and ADHD reflect different manifestations caused by a common shared susceptibility or mechanism (216). Subtle epileptic activity may also manifest as symptoms of ADHD (217), or ADHD symptoms could be due to side effects from AED treatment (215). We could not find that an association between epilepsy and ADHD in relation to pregnancy has been described in previous literature. As we only investigated ADHD during pregnancy, we do not know whether there was a change in

the prevalence of such symptoms compared to the period before the partner's pregnancy. The lower ADHD prevalence compared to other studies on non-pregnant persons with epilepsy may reflect that pregnancy typically occur during a stable period of life (215). Although there was no difference in ADHD screening symptoms between the expecting men with epilepsy and the reference group in paper II, there was a discrepancy between the self-reported diagnosis of ADHD and the diagnosis assessed through the ASRS-symptom score that applied for all the fathers in the cohort, the latter showing a much higher prevalence. This suggests that ADHD was under-reported in the general male population, similar to depression in the expecting women. Symptoms of ADHD can also overlap with depression and anxiety (215), and it could be that the specificity of the screening tool is too low, thereby incorrectly identifying screening positive ADHD.

Self-reported eating disorders were associated with epilepsy in women before pregnancy. For expecting fathers we found no difference between the epilepsy and reference groups. As eating disorders may affect fertility negatively (218) the prevalence was, as expected, low in all women during pregnancy, and we could not show any difference for a self-reported diagnosis of eating disorders between the women with epilepsy compared to the references. However, in a more recent study on the same population of women, we found that binge eating disorder, assessed by using DSM-IV criteria, was associated with epilepsy during pregnancy (219). This is similar to the pattern of discrepancy that was found between self-reported vs. screening positive diagnoses of depression in women (paper I) and ADHD in men (paper II). It could also be that the women did not recognize binge eating as an eating disorder, because eating disorders are typically associated with symptoms such as weight loss, intense fear of gaining weight, or vomiting, and not excessive food intake. Previous studies on eating disorders in patients with epilepsy are very sparse, and mostly limited to case reports or related to specific AED use, such as topiramate (220, 221). One population based study by Rai *et al.* found a threefold increase of eating disorders in non-pregnant persons with epilepsy compared to persons without epilepsy and compared to other chronic disorders (67). However, eating disorders in pregnant persons with epilepsy have previously been unexplored. Eating disorders are related to

other psychiatric comorbidity, such as affective and anxiety disorders (222, 223). This association could partly explain the increased ratio of eating disorders in women with epilepsy. Social stigma and low self-esteem, both associated with epilepsy, may also account for the correlation with eating disorders (223). Low or adverse socioeconomic status, aspects of which we found to be increased in epilepsy, represents a risk factor for an unhealthier life style (224). This can be due to lack of knowledge about dietary recommendations, and because of social influence and reduced financial resources. A clinical implication of discovering an increased risk of eating disorders in young women with epilepsy is a known association with risk of birth complications (219). In the epilepsy group, the finding that psychiatric comorbidity appeared to be underreported could be due to lack of recognition in the persons with epilepsy, as the symptoms of the psychiatric disorder may be perceived as a part of the epilepsy, instead of separate symptoms in need of adequate treatment. For all the persons in the cohort, it could be a result of deliberate underreporting as psychiatric disease is associated with shame and stigma.

Women with epilepsy experience specific concerns during and after pregnancy, such as administration of AED in pregnancy and during breastfeeding. Hormones affect serum levels of AEDs, lack of sleep may affect susceptibility to seizures, and being left alone with an infant may cause worries, anxiety and depression. Several of the adverse socioeconomic conditions that were increased in expecting parents with epilepsy may also partly explain their elevated emotional distress and psychological complaints compared to references without epilepsy. Single parenting was slightly more common in pregnant women with epilepsy, in line with previous research that has showed that women with epilepsy have more unplanned pregnancies (225). Additionally, mothers with epilepsy more frequently reported having ended their relationship at both 6 and 18 months postpartum. Preparing to become a mother can be stressing, and becoming a single mother even more so. Partner support is shown to be especially important in protecting against epilepsy specific concerns and mental complaints, irrespective of other types of social support (191, 192). This leaves single women with epilepsy at particular risk of mental complaints both during pregnancy and postpartum. Expecting fathers in our study were not registered as single, as their

participation primarily depended on the participation of their partner. Nevertheless, several other adverse socioeconomic aspects were associated with epilepsy in the men, and these aspects may represent risk factors for emotional complaints. The association between treatment dependent NNCD and mental health was also evaluated. Epilepsy came out worse for many aspects, showing that having epilepsy represents a particular strain.

Epilepsy is associated with adverse effects on pregnancy and birth outcome (128, 135, 136, 226). This is also true for psychiatric disease, as women with mental health problems less often attend prenatal care clinics, and also because of direct negative effects on delivery and child outcome (227). For instance, maternal anxiety affects foetal activity and heart rate, and mood disorders and eating disorders in pregnancy are associated with operative and preterm delivery, as well as foetal growth restriction (219, 227). Women with epilepsy and psychiatric comorbidity therefore should to be at particular risk of pregnancy and birth complications. We demonstrated that the expecting fathers with epilepsy also struggle more with psychiatric comorbidity and complaints during pregnancy. This can also affect the expecting mother, as partner support is particularly important during pregnancy, delivery, and postpartum. Fathers' mental health has been shown to be a protective factor against depression in both mother and child (228). Emotional health and wellbeing in the pregnant women is important for birth outcome (229). Psychiatric disorders in expecting women and men are a risk factor for postpartum depression in both genders (203, 204, 227, 230). The higher frequency of psychiatric comorbidity in men and women with epilepsy during pregnancy should therefore be considered as an important indication of elevated risk of psychiatric complaints in the postpartum period. Such persons should be identified prior to pregnancy if possible, and be offered proper treatment and follow up.

5.2.4 Quality of life and self-esteem

Pregnancy and relationship status are probably the most important explanations for the overall high satisfaction with life found in all the study populations. Pregnancy is

typically associated with positive expectations about the baby and family life, and the majority of the participants in our study were in a relationship. As mentioned earlier, having a partner is important for quality of life and feeling of security, and particularly in persons with epilepsy (191, 192). High relationship satisfaction, life satisfaction and self-esteem are also previously shown to be important as buffer against affective distress, and can enhance remission from pre-pregnancy psychiatric disorders (184, 231, 232). Nevertheless, our results from paper II and III on life satisfaction and self-esteem in men and women with epilepsy showed that they were less satisfied than the references without epilepsy. Our findings in paper I and II, as well as our own work in an additional paper on the women in MoBa (168), show that depression was more common in both genders with epilepsy during and after pregnancy, and depression is one of the strongest predictors of quality of life in epilepsy (195). Anxiety and perceived stigma can be social hinders, which worsen social isolation, and thereby also affect quality of life negatively (195). Sick leave and unemployment also increase social isolation. At 18 months postpartum most parents are expected to return to be back in work after parental leave. The finding that fewer mothers with than without epilepsy were in a job at this point of time could reflect a delay in convalescence. At 18 months postpartum, experiencing low general self-efficacy was also more common among mothers with epilepsy than the references. Knowledge about epilepsy is significant for high levels of self-efficacy, whereas seizures are negatively correlated with both self-efficacy and depression in epilepsy (233). Low self-efficacy in epilepsy is also a risk factor for depression (234, 235). The overall impact of adverse socioeconomic challenges and adverse life events such as serious illness or injuries, more frequently reported by women with epilepsy, could negatively affect timing of return to work, and cause more affective distress in women 18 months postpartum. These conditions may also account for the lower satisfaction with life and self-esteem during pregnancy in both women and men with epilepsy. The various factors are obviously intertwined and causations are challenging to establish. Our point was, however, not to determine causations, but to promote the understanding of potential risk factors for mental health and quality of life in pregnant persons with epilepsy.

6. Conclusions

The work in this thesis demonstrates that women and men with epilepsy are at higher risk of psychiatric disorders and complaints, adverse social aspects and lower quality of life during and after pregnancy compared to persons without epilepsy. Adverse socioeconomic conditions account for a part of the observed difference in comorbid mood disorders. The burden of living with at a chronic disease seems partly to explain the higher risk of poorer psychosocial conditions, but several risks are epilepsy-specific.

Among pregnant women, those with epilepsy and psychiatric comorbidity are regarded extra vulnerable, as both conditions separately increase the risk of pregnancy and birth complications. Early identification of mood complaints in this group of women is therefore particularly important.

The increased risks of mental complaints and social conditions in expecting men with epilepsy compared to men without epilepsy deserve more attention. Fathers' involvement and role as active caretaker during pregnancy and parental leave is increasingly important in modern society, and their health affect both their partners and children.

Our results indicate that psychiatric disorders are underreported in the general population of pregnant women and men. This implies that persons in need of extra follow up and treatment miss out on important care during pregnancy. Psychiatric disorders during pregnancy are known predictors of poorer mental health postpartum in both genders, leaving expecting mothers and fathers with epilepsy and psychiatric comorbidity at extra risk of adverse life aspects after pregnancy. An important sign of disease burden is our finding that women with epilepsy are at higher risk of unemployment and lower self-efficacy compared to women without epilepsy after the postpartum period.

Pre-pregnancy counselling for women and men with epilepsy should include use of screening instruments for psychiatric symptoms, quality of life and questions about

socioeconomic conditions. This is a discrete and cost-effective intervention without pathologizing otherwise healthy individuals. Early identification of patients at risk could prevent long-term effects from poor psychological health.

7. References

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8. Appendices

Appendix I. Variables in screening instruments and single questions used to assess psychiatric symptoms and different aspects of satisfaction with life (translation from Norwegian by the Norwegian Institute of Public Health).

Appendix II. Example of questions from MoBa-questionnaire (translation from Norwegian by the Norwegian Institute of Public Health).

Appendix III. Example of information from Medical Birth Registry of Norway (Norwegian)

Appendix I. Variables in screening instruments and single questions used to assess psychiatric symptoms and different aspects of satisfaction with life (translation from Norwegian by the Norwegian Institute of Public Health).

Life Time Major Depression	**Response options**
Have you ever experienced the following for a period of 2 weeks or more?:	
1. Felt depressed, sad	No/ Yes
2. Had problems with appetite or eaten too much	No/ Yes
3. Been bothered by lack of energy	No/ Yes
4. Blamed yourself and felt worthless	No/ Yes
5. Had problems with concentration or had problems making decisions	No/ Yes
6. Had at least 3 of the problems named above simultaneously	No/ Yes
7. Was there a particular reason for this?	No/ Yes

Hopkins Symptom Checklist	**Response options**
Have you been bothered by any of the following during the past two weeks?:	
1. Feeling fearful	4 (1-4)
2. Nervousness or shakiness inside	4 (1-4)
3. Feeling hopeless about the future	4 (1-4)
4. Feeling blue	4 (1-4)
5. Worrying too much about things	4 (1-4)
6. Feeling everything is an effort*	4 (1-4)
7. Feeling tense or keyed up*	4 (1-4)
8. Suddenly scared for no reason*	4 (1-4)
Response option 1-4: “Not bothered”, “A little bothered”, “Quite bothered”, “Very bothered”.	
*Question 6-7 did not exist in the women’s questionnaire 1 and could therefore not be assessed in paper I and paper III.	

Adult ADHD Self Report Scale	Response options
Feeling of anxiety and restlessness in the last six months:	
1. How often do you have problems completing the final aspects of a task when the challenging part is already done?	5 (1-5)
2. How often do you have problems putting things in the right order when you are involved in tasks that require organization?	5 (1-5)
3. When you have a task which requires a great deal of careful preparation, how often do you avoid or put off starting it?	5 (1-5)
4. How often do you have problems remembering appointments or duties?	5 (1-5)
5. When you have to sit still for a long time, how often do you move your hands and feet in an agitated and restless way?	5 (1-5)
6. How often do you feel hyperactive and obliged to do things, as if you are being driven by an machine?	5 (1-5)
Response option 1-5: “Never”, “Seldom”, “Sometimes”, “Often”, “Very often”	

Rosenberg´s Self-Esteem Scale	Response options
What kind of perception do you have of yourself?:	
1. I have a positive attitude towards myself	4 (1-4)
2. I feel really useless at times	4 (1-4)
3. I feel that I don’t have much to be proud of	4 (1-4)
4. I feel that I’m a valuable person, on an equal footing with anyone else, at any rate	4 (1-4)
Response option 1-4: “Strongly agree”, “Agree”, “Disagree”, “Strongly disagree”	

Relationship Satisfaction	Response options
How well do these statements describe your relationship?:	
1. I have a close relationship with my spouse/partner	6 (1-6)
2. My partner and I have problems in our relationship	6 (1-6)
3. I am very happy with our relationship	6 (1-6)
4. My partner is generally understanding	6 (1-6)
5. I often consider ending our relationship	6 (1-6)
6. I am satisfied with my relationship with my partner	6 (1-6)
7. We frequently disagree on important decisions	6 (1-6)
8. I have been lucky in my choice of a partner	6 (1-6)
9. We agree on how our child should be raised	6 (1-6)
10. I believe my partner is satisfied with our relationship	6 (1-6)
Response option 1-6: “Agree completely”, “Agree”, “Agree somewhat”, “Disagree somewhat”, “Disagree”, “Disagree completely”	

Satisfaction with life scale	Response options
Do you agree or disagree with the following statements?:	
1. My life is largely what I wanted it to be	7 (1-7)
2. My life is very good	7 (1-7)
3. I am satisfied with my life	7 (1-7)
4. To date, I have achieved what is important for me in my life	7 (1-7)
5. If I could start all over, there is very little I would do differently	7 (1-7)
Response option 1-7: “Agree completely”, “Agree”, “Agree somewhat”, “Disagree somewhat”, “Disagree”, “Disagree completely”	

World Health Organization's Quality of Life instrument-short version	Response options
How would you rate your quality of life?	5 (1-5)
Response option 1-5:"Very poor", "Poor", "Neither poor nor good", "Good", "Very good"	
How satisfied are you with your health?	5 (1-5)
Response option 1-6: "Very dissatisfied", "Dissatisfied", "Neither satisfied nor dissatisfied", "Satisfied", "Very satisfied"	

The General Self-Efficacy Scale	Response options
How well do these statements describe you?	
1. I can always manage to solve difficult problems if I try hard enough	4 (1-4)
2. If someone opposes me, I can find the means and ways to get what I want	4 (1-4)
3. I am confident that I could deal efficiently with unexpected events	4 (1-4)
4. I can remain calm when facing difficulties because I can rely on my coping abilities	4 (1-4)
5. If I am in trouble, I can think of a good solution	4 (1-4)
Response option 1-4: "Not at all true", "Hardly true", "Moderately true", "Exactly true"	

Work strains	Response options
How do the following statements describe your work situation?	
1. My work is very stressful	4 (1-4)
2. I learn a lot at work	4 (1-4)
3. My work is very monotonous	4 (1-4)
4. I am able to decide how my work is to be carried out	4 (1-4)
5. There is a good team spirit at my place of work	4 (1-4)
6. I enjoy my work	4 (1-4)
Response option 1-4: "Agree", "Agree mostly", "Disagree mostly", "Disagree"	

Life events	Response options
Have you experienced any of the following during the last 12 months?	
1. Problems at work	
2. Financial problems	No/ Yes
3. Divorce/separation	No/ Yes
4. Conflicts with family/friends/neighbours	No/ Yes
5. Concerns about the baby	No/ Yes
6. Serious personal injury/illness	No/ Yes
7. Close relative being injured/ill	No/ Yes
8. Involved in traffic accident/fire/robbery	No/ Yes
9. Lost someone close	No/ Yes
10. Exposed to physical violence.	No/ Yes

Social support	Response options
1. *Do you have anyone other than your husband/partner you can ask for advice in a difficult situation?* Response option 1-3: "No", "Yes, 1 or 2 people", "Yes, more than 2 people"	3 (1-3)
2. *How often do you meet or talk on the telephone with your family (other than your husband/partner and children) or close friends?* Response option 1-3: "Once a month or less", "2-8 times a month", "More than twice a week"	3 (1-3)
3. *Do you often feel lonely?* Response option 1-5: «Almost never", "Infrequently", "Sometimes", "Usually", "Almost always"	5 (1-5)

Appendix II

Example of questions from MoBa-questionnaire (translation from Norwegian by the Norwegian Institute of Public Health).

Previous and current illnesses and health problems

39. Do you have or have you had any of the following illnesses or health problems? If you have taken medication (tablets, mixtures,suppositories, inhalers, creams, etc.) in conjunction with the illness or health problem give the name(s) of the medication(s) and when you took them.

Illness/health problem during this pregnancy			Use of medication						
Illness/health problem	Before Pregnancy	During Pregnancy	Name of medicines	Last 6 months before pregnancy	Pregnancy week 0-4	5-8	9-12	13+	Number of days used
Other illnesses/health problems									
44 Anorexia/bulimia/other eating disorders	☐	☐		☐	☐	☐	☐	☐	
45 Migraine	☐	☐		☐	☐	☐	☐	☐	
46 Other headache	☐	☐		☐	☐	☐	☐	☐	
47 Epilepsy	☐	☐		☐	☐	☐	☐	☐	
48 Multiple sclerosis	☐	☐		☐	☐	☐	☐	☐	
49 Cerebral palsy	☐	☐		☐	☐	☐	☐	☐	
50 Cancer	☐	☐		☐	☐	☐	☐	☐	
51 Depression	☐	☐		☐	☐	☐	☐	☐	
52 Anxiety	☐	☐		☐	☐	☐	☐	☐	
53 Other long illness or health problems	☐	☐		☐	☐	☐	☐	☐	
Which									

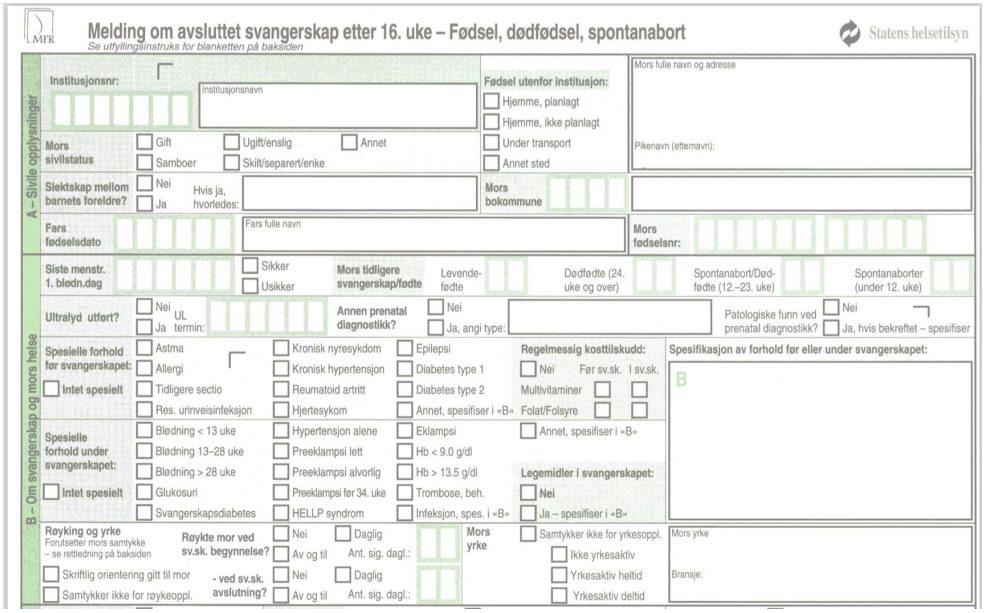
Other medicines

44. Have you used other medication not previously mentioned? If yes, which and when did you take them?

Name of medication (e.g. Valium, Rohypnol, Paracetamol)	Use of medication during pregnancy weeks: Last 6 months before pregnancy	0-4	5-8	9-12	13+	Number of days used
	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	
	☐	☐	☐	☐	☐	

Appendix III

Example of information from Medical Birth Registry of Norway (Norwegian)



Melding om avsluttet svangerskap etter 16. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

Statens helsetilsyn

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn | Fødsel utenfor institusjon: Hjemme, planlagt; Hjemme, ikke planlagt; Under transport; Annet sted | Mors fulle navn og adresse | Pikenavn (etternavn):

Mors sivilstatus: Gift; Samboer; Ugift/enslig; Skilt/separert/enke; Annet

Slektskap mellom barnets foreldre? Nei; Ja. Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato | Fars fulle navn | Mors fødselsnr:

B – Om svangerskap og mors helse

Siste menstr. 1. blødn.dag | Sikker; Usikker

Mors tidligere svangerskap/fødte: Levendefødte | Dødfødte (24. uke og over) | Spontanabort/Dødfødte (12.–23. uke) | Spontanaborter (under 12. uke)

Ultralyd utført? Nei; Ja. UL termin:

Annen prenatal diagnostikk? Nei; Ja, angi type:

Patologiske funn ved prenatal diagnostikk? Nei; Ja, hvis bekreftet – spesifiser

Spesielle forhold før svangerskapet: Intet spesielt; Astma; Allergi; Tidligere sectio; Res. urinveisinfeksjon; Kronisk nyresykdom; Kronisk hypertensjon; Reumatoid artritt; Hjertesykom; Epilepsi; Diabetes type 1; Diabetes type 2; Annet, spesifiser i «B»

Regelmessig kosttilskudd: Nei; Før sv.sk.; I sv.sk.; Multivitaminer; Folat/Folsyre

Spesifikasjon av forhold før eller under svangerskapet: B

Spesielle forhold under svangerskapet: Intet spesielt; Blødning < 13 uke; Blødning 13–28 uke; Blødning > 28 uke; Glukosuri; Svangerskapsdiabetes; Hypertensjon alene; Preeklampsi lett; Preeklampsi alvorlig; Preeklampsi før 34. uke; HELLP syndrom; Eklampsi; Hb < 9.0 g/dl; Hb > 13.5 g/dl; Trombose, beh.; Infeksjon, spes. i «B»; Annet, spesifiser i «B»

Legemidler i svangerskapet: Nei; Ja – spesifiser i «B»

Røyking og yrke. Forutsetter mors samtykke – se rettledning på baksiden

Røykte mor ved sv.sk. begynnelse? Nei; Daglig; Av og til; Ant. sig. dagl.:

- ved sv.sk. avslutning? Nei; Daglig; Av og til; Ant. sig. dagl.:

Skriftlig orientering gitt til mor

Samtykker ikke for røykeoppl.

Mors yrke: Samtykker ikke for yrkesoppl.; Ikke yrkesaktiv; Yrkesaktiv heltid; Yrkesaktiv deltid

Mors yrke | Bransje:

9. Original publications

I

Paper I

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Psychiatric comorbidity and social aspects in pregnant women with epilepsy — The Norwegian Mother and Child Cohort Study

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ABSTRACT

Objective: The objective of this study was to investigate psychiatric disease and social aspects in young women with epilepsy before and during pregnancy.
Method: The study included self-reported data from 106,935 pregnancies.
Results: Seven hundred eleven women reported having epilepsy, and 45.9% of them were using antiepileptic drugs (AEDs). Compared to the reference group, self-reported eating disorders and depression were increased in the untreated epilepsy group before pregnancy. Both AED-treated and untreated women with epilepsy reported higher depression scores as assessed by the Hopkins Symptom Checklist, and the Lifetime Major Depression scale was increased in AED-treated women. Antiepileptic drug treatment was linked to low income (27.4% vs. 18.4%, $p < 0.001$) and no income (5.5% vs. 2.6%, $p = 0.001$). Low educational level was associated with epilepsy in AED-treated and untreated women (50.5%, $p < 0.001$ and 46.9%, $p < 0.001$ vs. 32.2%), as was unemployment due to disability (7.9%, $p < 0.001$ and 6.5%, $p < 0.001$ vs. 1.5%) and single parenting (4.4%, $p = 0.016$ and 4.5%, $p = 0.007$ vs. 2.4%). No difference was found for smoking, alcohol use, or narcotic use.
Conclusion: Symptoms of depression were associated with epilepsy both during and before pregnancy. Epilepsy was linked to eating disorders before pregnancy. Unemployment, single parenting, and low educational level were linked to epilepsy in young pregnant females. Efforts aiming at treatment and screening for psychiatric comorbidity in pregnant women with epilepsy are important in the follow-up of these patients.

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1. Introduction

Epilepsy is a common disorder with a lifetime population prevalence of 0.6% in developed countries and 1.5% in developing countries [1]. Single epileptic seizures occur in 10% of the population. Epilepsy is caused by a combination of underlying pathological processes and genetic factors. Epilepsy is also a common disorder in pregnancy, occurring in 0.3–0.7% [2,3].

Epilepsy is associated with an increased prevalence of psychiatric comorbidity and poor mental health [4,5], and this association seems to be stronger than for other chronic and somatic disorders [6]. Depression is the most common psychiatric disease in epilepsy [7], with a reported prevalence ranging from 20% to 70% [7–9]. Other psychiatric disorders also occur more frequently than expected [6,10,11]. The question of whether epilepsy predisposes individuals to psychiatric disorders or vice versa has stimulated studies on joint underlying genetic and structural mechanisms [10,12,13]. Drugs given to prevent epileptic seizures are also used to treat mood disorders, anxiety, obsessive–compulsive disorders, and schizophrenia [14,15]. In contrast, antiepileptic drugs (AEDs) can lead to psychiatric symptoms, and an increased suicide risk has been reported for some of the drugs [16,17].

Epilepsy has an adverse effect on quality of life [18,19]. The condition has been associated with social stigma, which can affect both psychosocial function and social status [20,21]. Treatment and seizure frequency are important determinants, as are concerns about side effects from AEDs and family planning [22,23]. When AED treatment is successful, most patients seem to score within the normal range of social well-being [23,24]. Low educational level and low income have been reported with higher frequency in populations with epilepsy [25,26], and persons with epilepsy are also less successful in finding and keeping employment [27,28].

Pregnant women with epilepsy are at a higher risk of gestational and birth complications than women without epilepsy [29]. Contraceptive failure and ectopic pregnancies are more common among women with epilepsy [30]. Pregnancy can affect the metabolism of AEDs and seizure control [31]. Pregnant women with epilepsy sometimes face difficult choices considering AED treatment. Antiepileptic drugs may have either established or potential teratogenic effects [32], while on

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Table 1
Variables used for the Lifetime Major Depression scale and the short version of Hopkins Symptom Checklist, with the number of response options.

Variables	Response options
Lifetime Major Depression scale[a]	
Have you ever experienced the following for a period of 2 weeks or more?	
Felt depressed, sad	No/yes
Had problems with appetite or eaten too much	No/yes
Been bothered by lack of energy	No/yes
Blamed yourself and felt worthless	No/yes
Had problems with concentration or had problems making decisions	No/yes
Had at least 3 of the problems named above simultaneously	No/yes
Was there a particular reason for this?	No/yes
Hopkins Symptom Checklist[a]	
Have you been bothered by any of the following during the last two weeks?	
Constantly frightened or anxious	4 (1–4)[b]
Nervous, inner turmoil	4 (1–4)[b]
Feeling of hopelessness with regard to the future	4 (1–4)[b]
Depressed, sad	4 (1–4)[b]
Frequently worried or uneasy	4 (1–4)[b]

[a] Cronbach's alpha for the LTMD scale and HSCL are 0.82 and 0.80, respectively.
[b] Response options 1–4: "Not bothered", "A little bothered", "Quite bothered", and "Very bothered".

the other hand, lack of seizure control may harm both the mother and the fetus [31]. Studies comparing mental health in women with epilepsy prior to and during gestation are practically missing, whereas an increased frequency of postpartum depression [33,34] and birth anxiety [35] has been reported in epilepsy.

Studies on psychiatric comorbidity and social aspects in pregnant women with epilepsy are sparse. Further, small study cohorts and potential selection bias are limitations in previous research. Representative cohorts including persons with both treated (active) and untreated (inactive) epilepsy should be examined. The Norwegian Mother and Child Cohort Study (MoBa) is a national prospective cohort of more than 100,000 participants, with detailed self-reported health data [36,37] and less selection bias compared to hospital-based cohorts. A recent validation study on MoBa showed that 89.5% of all the women with untreated epilepsy had inactive epilepsy, defined by the absence of epileptic seizure during the last five years [38]. The cohort gives a unique opportunity to examine comorbidity and social aspects in young women before and during pregnancy, a vulnerable group.

The main aims in the present study were to (1) examine the association between mental disorders in women with epilepsy prior to and during pregnancy in a large population-based cohort, (2) investigate social aspects in the same women during pregnancy, and (3) compare AED-treated and untreated groups of pregnant women with epilepsy.

2. Material and methods

2.1. Data collection and assessment of epilepsy

The Norwegian Mother and Child Cohort Study (MoBa) was established with the purpose of collecting data from at least 100,000 pregnancies to study causes of disease [37]. Inclusion was made from June 1999 to December 2008. Pregnant women examined at hospitals and maternity units with more than 100 births annually were invited to participate, with the inability to speak Norwegian being the only exclusion criterion. The women received a postal invitation prior to their scheduled ultrasound scanning at pregnancy weeks 13–17 [37]. Women with miscarriages prior to the routine ultrasound examination were not included, with the exception of women who had consented to participate prior to their miscarriage. Mothers have contributed data from a self-reported questionnaire filled in at pregnancy weeks 13–17, 22, and 30 and several times after giving birth. The response rate among those invited was 38.5%. In a validation study, it was concluded that prevalence estimates of exposures and outcomes, but not estimates of exposure-outcome associations are biased due to self-selection in the Norwegian Mother and Child Cohort Study [39]. We presume that potential selection bias is the same for the group with epilepsy and the reference group and, therefore, that comparisons between the groups are valid. The prevalence of epilepsy in MoBa was as expected, i.e., 0.7% (Table 2).

Only data reported during gestational weeks 13–17 were applied in this study, including information on general health, education, occupation, home conditions, lifestyle, and medications. Social aspects were reported as present during the pregnancy, except for narcotic use (numbers during pregnancy are too small to examine). Psychiatric diagnoses were categorized as 'prior to pregnancy' and 'during pregnancy'. The questionnaire contained 137 questions, mostly with predefined responses but some with open-ended answers. Data on medication were coded according to the Anatomical Therapeutic Chemical (ATC) Classification System, consisting of a five-digit ATC number [40].

Our study was a cross-sectional prevalence study based on version 5 of the quality-assured data files released for research on epilepsy and included 106,935 pregnancies (Fig. 1). For women who enrolled more than once, each pregnancy was registered. A unique identification number used in both MoBa and the compulsory Medical Birth Registry of Norway (MBRN) made it possible to link the two registries and attain supplementary information. Information on epilepsy and AED treatment is compulsory in MBRN and is recorded by health personnel.

All mothers in MoBa who reported being diagnosed with epilepsy prior to or during pregnancy were included in our population with epilepsy. In total, 634 mothers with epilepsy were registered with 711 pregnancies and compared to a reference group consisting of mothers without epilepsy (n = 106,224). The primary analyses included all recorded pregnancies. To account for the potential effects of repeated measures in the same women, the analyses were also performed

Table 2
Social characteristics of women with epilepsy who did and did not use antiepileptic drugs (AEDs) during pregnancy compared to the reference group.

	Reference group (n = 106,224)	Epilepsy all (n = 711, 0.7%)			Epilepsy with AED (n = 329, 0.3%)			Epilepsy without AED (n = 382, 0.4%)		
Characteristics	% (n)	% (n)	p-Value	OR (CI)	% (n)	p-Value	OR (CI)	% (n)	p-Value	OR (CI)
Mean age in years (SD)	29.8 (4.6)	29.2 (4.9)	0.005	NA	29.3 (4.9)	0.12	NA	29.2 (5.0)	0.017	NA
Low education (<12 years)	32.2 (34,179)	48.5 (345)	<0.001	2.0 (1.7–2.3)	50.5 (166)	<0.001	2.1 (1.7–2.7)	46.9 (179)	<0.001	1.9 (1.5–2.3)
Low income	18.4 (17,873)	23.9 (160)	<0.001	1.4 (1.2–1.7)	27.4 (84)	<0.001	1.7 (1.3–2.2)	21.0 (76)	0.20	1.2 (0.9–1.5)
No income	2.6 (2526)	4.3 (29)	0.005	1.7 (1.2–2.5)	5.5 (17)	0.001	2.2 (1.3–3.6)	3.3 (12)	0.39	1.3 (0.7–2.3)
Unemployed due to disability	1.5 (1634)	7.2 (51)	<0.001	4.9 (3.7–6.6)	7.9 (26)	<0.001	5.5 (3.7–8.2)	6.5 (25)	<0.001	4.4 (3.0–6.7)
Single parenting	2.4 (2362)	4.4 (31)	<0.001	1.9 (1.3–2.8)	4.4 (14)	0.017	1.9 (1.1–3.3)	4.5 (17)	0.006	2.0 (1.2–3.2)
Smoking during pregnancy	8.3 (8313)	10.0 (69)	0.12	1.2 (1.0–1.6)	11.4 (36)	0.049	1.4 (1.0–2.0)	8.8 (33)	0.74	1.1 (0.7–1.5)
Alcohol during pregnancy	2.3 (2480)	2.8 (20)	0.40	1.2 (0.8–1.9)	3.6 (12)	0.12	1.6 (0.9–2.8)	2.1 (8)	0.76	0.9 (0.4–1.8)
Narcotics prior to pregnancy	9.8 (10,417)	10.3 (73)	0.68	1.1 (0.8–1.3)	9.7 (32)	0.96	1.0 (0.7–1.4)	10.7 (41)	0.54	1.1 (0.8–1.5)

Unadjusted OR, odds ratio; CI, confidence interval; SD, standard deviation; NA, not applicable.

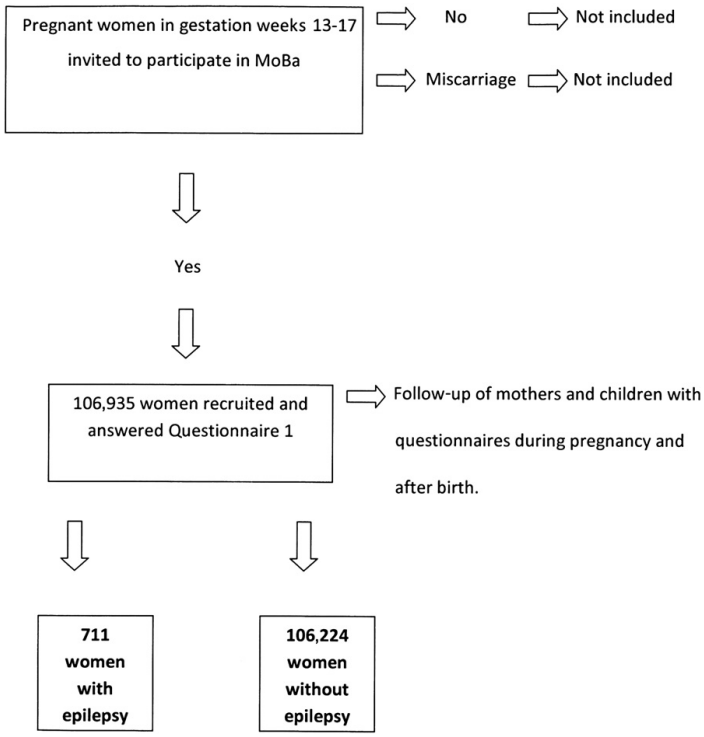

Fig. 1. Inclusion in the Norwegian Mother and Child Cohort Study (MoBa) (1999–2008) and the present cross-sectional prevalence study.

including only the 634 first recorded pregnancies (online-only supplementary material; e-Tables 1–4).

Antiepileptic drug use during pregnancy registered in MoBa, MBRN, or both, was recorded for the group with epilepsy. Antiepileptic drug use was stratified into four groups: polytherapy (n = 60) and three monotherapy groups: lamotrigine (LTG) (n = 103), valproate (VPA) (n = 40), and carbamazepine (CBZ) (n = 68). Other anticonvulsants registered as monotherapy were levetiracetam (n = 17), topiramate (n = 11), oxcarbazepine (n = 9), clonazepam (n = 7), phenytoin (n = 4), phenobarbital (n = 4), gabapentin (n = 2), primidone (n = 1), and clobazam (n = 1), as well as unspecified anticonvulsants (n = 2).

2.2. Variables

The main outcomes were as follows: 12 years or less of education, low income (19,000 euros or less yearly), no income (yes/no), unemployment due to disability (yes/no), single parenting (yes/no), smoking during pregnancy (yes/no), alcohol use during pregnancy (one or more occasions per month), and narcotic use before pregnancy (yes/no). Narcotics included cannabis, amphetamine, ecstasy, cocaine, and heroin. Low income was defined as a household income per consumption unit less than 60% of the median [41], i.e., <19,000 euros in our study.

Eating disorders, anxiety, and depression were the three psychiatric disorders predefined in the MoBa questionnaire. The diagnoses were assessed by answering yes or no prior to pregnancy and during pregnancy. Scores for the Lifetime Major Depression (LTMD) scale [42] and the short version of the Hopkins Symptom Checklist (HSCL) [43] for anxiety and depression were computed (Table 1). Lifetime Major Depression scale and the Hopkins Symptom Checklist were used to evaluate depressive symptoms prior to and during pregnancy, respectively. The proportion of scales with missing values was 8.6% for the HSCL and 9.0% for the LTMD scale. To avoid potential sample distortions, a maximum likelihood estimation procedure was applied to impute missing values [44]. Scores with ≥20% missing data were excluded.

2.3. Ethics

Informed consent was obtained from each MoBa participant upon recruitment. Data were recorded anonymously. Participation in MoBa was voluntary with the opportunity to withdraw from the study at any time. Our study was performed after the end of MoBa inclusion and had no effect on data collection. The study and research protocol were approved by the Regional Committee for Medical Research Ethics in Western Norway.

2.4. Statistics

Analyses were performed using SPSS Statistics 18.0 (SPSS Inc., Chicago, IL, USA). The group with epilepsy was compared to the reference group without epilepsy. Independent-samples *t*-test was conducted to compare the mean age for the groups. Dichotomous variables were analyzed by Pearson's chi-square test and by Fisher's exact test for cross-tabulations with an expected cell count of less than five. Results are presented as crude frequencies and unadjusted odds ratios (OR) with 95% confidence interval (CI) and corresponding p-values. Two-sided p-values <0.05 were considered statistically significant. When significant differences were found between the group with epilepsy and the reference group for psychiatric disease, binary logistic regression was performed to assess the impact of potential confounding factors. Age, level of education, level of income, no income, unemployment due to

Table 3
Risk of low income, low education, and unemployment in subgroups of AED-treated women with epilepsy compared to the reference group.

	Low income[a] (n = 18,033, 16.9%)			Low education[b] (n = 34,524, 32.3%)			Unemployment due to disability (n = 1685, 1.6%)		
Group	% (n)	p-Value	OR (CI)	% (n)	p-Value	OR (CI)	% (n)	p-Value	OR (CI)
Reference	18.4 (17,873)	NA	1	32.2 (34,180)	NA	1	1.5 (1634)	NA	1
Polytherapy	43.6 (24)	<0.001	3.4 (2.0–5.9)	55.0 (33)	<0.001	2.6 (1.5–4.3)	23.3 (14)	<0.001	19.5 (10.5–35.5)
Valproate[c]	14.3 (5)	0.53	0.7 (0.3–1.9)	47.5 (19)	0.038	1.9 (1.0–3.5)	5.0 (2)	0.13	3.4 (0.8–14.0)
Carbamazepine[c]	23.9 (16)	0.24	1.4 (0.8–2.4)	54.4 (37)	<0.001	2.5 (1.6–4.1)	2.9 (2)	0.28	1.9 (0.4–7.9)
Lamotrigine[c]	27.6 (27)	0.019	1.7 (1.1–2.6)	47.6 (49)	0.001	1.9 (1.3–2.9)	5.8 (6)	<0.005	4.0 (1.7–9.0)

Unadjusted OR, odds ratio; CI, confidence interval; SD, standard deviation; NA, not applicable.
[a] Annual income < 19,000 euros.
[b] Education of 12 years or less.
[c] Monotherapy.

disability, and single parenting were included. Unadjusted risks were generally preferred as our main aim was to assess associations, not to identify the causations.

3. Results

Among all mothers in MoBa, 0.7% reported having epilepsy (Table 2). Among them, 45.9% were treated with AEDs, with the majority using monotherapy (81.5%). Only 0.036% (n = 39) of the women in the MoBa cohort used AEDs during pregnancy for reasons other than epilepsy, including depression, anxiety, pain, cerebral palsy, MS, migraine, or other types of headache. Excluding such pregnancies had a minimal effect on the risk estimates in the group with epilepsy.

3.1. Psychiatric disease

Current or previous psychiatric disease, including depression, anxiety, or eating disorders, was reported by 10.1% (n = 10,810) of all women in MoBa. The frequency was higher among women with epilepsy compared to the reference group (13.4% vs. 10.1%, OR = 1.4, CI = 1.1–1.7, p = 0.004). In the group with epilepsy, 16.2% of untreated (OR = 1.7, CI = 1.3–2.3, p < 0.001) and 10.0% of AED-treated women (OR = 0.99, CI = 0.69–1.4, p = 0.97) reported some type of psychiatric disease either before or during pregnancy. Women undergoing AED polytherapy had the highest frequency of psychiatric disorders (16.7%, OR = 1.8, CI = 0.90–3.5, p = 0.091).

Self-reported depression was the most common psychiatric disorder reported both prior to and during pregnancy, and it was significantly increased in women with epilepsy before pregnancy (Table 4), mainly due to an increase among untreated women with epilepsy (9.9% vs. 6.2% in the reference group). Among the AED subgroups, depression was reported with the highest frequency in the polytherapy group, 11.7% and 5.0% prior to and during pregnancy, respectively. The association between epilepsy and depression was not significant after adjustment for confounders (age, level of education, income, unemployment, single parenting, and parity). Depression showed the strongest association with unemployment and then with single parenting.

Anxiety was reported with an increased frequency in untreated women with epilepsy prior to pregnancy (Table 4), but it was not significantly increased for any of the treatment subgroups. The association was not consistent after logistic regression. The frequency of eating disorders was also increased in the group with epilepsy before pregnancy, again due to a marked increase among the untreated group (Table 4), which was also significant after adjustment for potential confounders (OR = 1.9, CI = 1.3–2.9, p = 0.002). Observations were too few to compare therapy subgroups.

During the 2nd trimester, both AED-treated and untreated women with epilepsy reported higher HSCL depression scores than women without epilepsy (Table 5), significant for the polytherapy and LTG groups and consistent for AED-treated women after logistic regression (OR = 1.5, CI = 1.1–2.1, p = 0.009). Similarly, scores for the LTMD scale was increased in AED-treated women with epilepsy, with the

Table 4
Self-reported depression, anxiety, and eating disorders before and during pregnancy. All groups with epilepsy are compared to the reference group.

	Before pregnancy			During pregnancy		
Group	% (n)	p-Value	OR (CI)	% (n)	p-Value	OR (CI)
Depression						
Reference	6.2 (6595)	NA	1	2.4 (2554)	NA	1
Epilepsy	9.0 (64)	0.002[a]	1.5 (1.2–1.9)	2.7 (19)	0.64	1.1 (0.7–1.8)
AED	7.9 (26)	0.20	1.3 (0.9–1.9)	2.4 (8)	0.97	1.0 (0.5–2.0)
No AED	9.9 (38)	0.003[a]	1.7 (1.2–2.3)	2.9 (11)	0.55	1.2 (0.7–2.2)
Anxiety						
Reference	3.4 (3604)	NA	1	1.5 (1564)	NA	1
Epilepsy	4.6 (33)	0.067	1.4 (1.0–2.0)	1.7 (12)	0.64	1.1 (0.7–2.0)
AED	3.6 (12)	0.80	1.1 (0.6–1.9)	1.8 (6)	0.49	1.2 (0.6–2.8)
No AED	5.5 (21)	0.023[a]	1.7 (1.1–2.6)	1.6 (6)	0.87	1.1 (0.5–2.4)
Eating disorders[b]						
Reference	2.9 (3070)	NA	1	0.3 (363)	NA	1
Epilepsy	4.8 (34)	0.003[a]	1.7 (1.2–2.4)	0.4 (3)	0.53	1.2 (0.4–3.9)
AED	2.4 (8)	0.62	0.8 (0.4–1.7)	0.0 (0)	NA	NA
No AED	6.8 (26)	<0.001[c]	2.4 (1.6–3.6)	0.8 (3)	0.15	2.3 (0.7–7.2)

Unadjusted OR, odds ratio; CI, confidence interval; SD, standard deviation; NA, not applicable.
[a] Significant difference from the reference group. Association does not persist after covariate adjustment.
[b] Anorexia nervosa, bulimia, or other eating disorders.
[c] Significant difference from the reference group. Association persists after covariate adjustment.

Table 5
Depression as indicated by the Hopkins Symptom Checklist[a] and the Lifetime Major Depression scale[b] scores among pregnant women with epilepsy compared to the reference group without epilepsy.

	Depression during pregnancy[a]			Earlier major depression[b]		
Group	% (n)	p-Value	OR (CI)	% (n)	p-Value	OR (CI)
Reference	10.8 (10,579)	NA	1	5.6 (5568)	NA	1
Epilepsy	16.4 (112)	<0.001[c]	1.6 (1.3–2.0)	7.0 (48)	0.11	1.3 (0.9–1.4)
AED	19.4 (60)	<0.001[c]	2.0 (1.5–2.7)	9.0 (28)	0.009[d]	1.7 (1.1–2.5)
No AED	14.0 (52)	0.045[d]	1.3 (1.0–1.8)	5.3 (20)	0.83	1.0 (0.6–1.5)
Polytherapy	22.4 (13)	0.004[d]	2.4 (1.3–4.4)	12.1 (7)	0.040[d]	2.4 (1.1–5.2)
Valproate[e]	16.2 (6)	0.28	1.6 (0.7–3.9)	8.3 (3)	0.45	1.5 (0.5–5.0)
Lamotrigine[e]	18.6 (18)	0.013[d]	1.9 (1.1–3.2)	10.0 (10)	0.057	1.9 (1.0–3.6)
Carbamazepine[e]	17.5 (11)	0.086	1.8 (0.9–3.4)	6.2 (4)	0.78	1.1 (0.4–3.1)

Unadjusted OR, odds ratio; CI, confidence interval; SD, standard deviation; NA, not applicable.
[a] Hopkins Symptom Checklist, pregnancy weeks 13–17.
[b] Lifetime Major Depression Scale.
[c] Significant difference from the reference group. Association persists after covariate adjustment.
[d] Significant difference from the reference group. Association does not persist after covariate adjustment.
[e] Monotherapy.

highest scores for the polytherapy group (Table 5), and this increase was also significant after adjustment for confounders (OR = 1.5, CI = 1.0–2.2, p = 0.045).

3.2. Social characteristics during pregnancy

Both AED-treated and untreated women with epilepsy reported a high frequency of adverse social aspects (Table 2). Education of 12 years or less was reported significantly more often among both AED-treated and untreated women with epilepsy than in the reference group without epilepsy (Table 2) and increased for both the polytherapy group and in the group undergoing monotherapies with LTG, CBZ, and VPA (Table 3).

An annual income of less than 19,000 euros was more common among women with epilepsy treated with AEDs (Tables 2 and 3). 'No income' was also more common among AED-treated women (Table 2), especially in the LTG group where this was reported by 7.1% (OR = 2.9, CI = 1.3–6.2, p = 0.014). The group with untreated epilepsy did not differ significantly from the reference group.

Unemployment due to disability was higher among women with epilepsy, especially for AED-treated women (Tables 2 and 3). In the polytherapy group, the rate of unemployment due to disability was 23.3% (Table 3).

Both AED-treated and untreated women with epilepsy were more often recorded as a single parent than the women in the reference group (Table 2), with 8.3% in the polytherapy group (OR = 3.8, CI = 1.5–9.4, p = 0.01) and 7.0% in the LTG group (OR = 3.1, CI = 1.4–6.7, p = 0.010).

Smoking was slightly more common among AED-treated women compared to the reference group, while alcohol consumption during pregnancy was similar for women with epilepsy and the reference group (Table 2). Alcohol use was the highest in the VPA group with a frequency of 7.5% (OR = 3.4, CI = 1.0–11.0, p = 0.066). For the polytherapy, CBZ, and LTG groups, the frequencies were 3.3%, 2.9%, and 3.9%, respectively. Use of narcotics before pregnancy was similar for AED-treated and untreated women with epilepsy and for the reference group (Table 2): 13.3% in the polytherapy group, 7.4% in the CBZ group, and 11.7% in the LTG group.

3.3. Repeated pregnancies

To evaluate the potential effects of repeated pregnancies, all the outcomes in the group with epilepsy vs. the reference group were analyzed for only the first recorded pregnancy. The risk estimates were generally very similar to the primary analyses and altogether strengthened (e-Tables 1–4). By this, we have shown that repeated pregnancies in the same women had minimal effect on our main outcomes.

4. Discussion

4.1. Key findings

Self-reported depression was not more frequent during pregnancy in women with epilepsy compared to the reference group. However, symptoms that indicate depression in validated checklists were increased. The polytherapy group had the highest frequency of psychiatric disorders and complaints. Depression, anxiety, and eating disorders occurred with an increased frequency in untreated women with epilepsy prior to pregnancy. This was consistent for eating disorders after adjusting for confounding factors. Adverse social aspects, such as low education, low income, and unemployment, were associated with both treated and untreated epilepsy and were most pronounced in the polytherapy group.

4.2. Strengths and limitations

Data were collected from a national cohort of pregnant women recruited from the general population, including women with both active and inactive epilepsy, without the selection bias associated with hospital-based populations and with a large reference group. A broad spectrum of socioeconomic information was available, facilitating the evaluation of confounders. Main outcomes could be compared for relevant AED-treated subgroups. A high validity (near 100%) of the self-reported epilepsy diagnosis, as well as of the reported AED use during pregnancy, has recently been found [38]. The untreated mothers generally had inactive epilepsy. The three self-reported main psychiatric diagnoses have not been validated but were supplemented by scores from two relevant and validated symptom tests (HSCL and LTMD scale).

The present study is cross-sectional and mainly based on observational data. Therefore, we cannot draw any firm conclusions about causations. Recall bias is a concern in all surveys based on self-reported data. The differences between the epilepsy group and the reference group regarding adverse social aspects should be the same irrespective of pregnancy. The prevalence of epilepsy in the MoBa cohort was as expected in a young female population [1]. The MoBa data have been demonstrated to estimate exposure–outcome associations without bias due to self-selection [39].

4.3. Interpretation

The frequency of reported psychiatric comorbidity in the present study was lower than those in previous reports [8,9], probably because

of methodological differences including study design, selection bias, and diagnostic tools [45]. Our findings of less psychiatric disease during than before pregnancy in the group with epilepsy may also reflect improved treatment and follow-up in pregnancy, as well as the women being in an optimal phase concerning sleep, nutrition, and alcohol use during pregnancy. Another plausible explanation for the modest prevalence of psychiatric disorders is that women with epilepsy who become pregnant are, in general, at better health than women with epilepsy who do not become pregnant. Since studying selected patient cohorts overestimates psychiatric comorbidity [45], our results probably reflect a more accurate frequency for young females with epilepsy.

The finding that untreated women with epilepsy reported more psychiatric disorders than those who were AED-treated was surprising. Less severe epilepsy without the need for treatment would be expected to have less comorbidity. An explanation could be that AEDs have a positive, modulating effect on psychiatric comorbidity. Several AEDs are prescribed for the treatment of mood, obsessive–compulsive, and anxiety disorders [14,15]. Women with more severe epilepsy could have related their depression and anxiety symptoms to their epilepsy and may have not reported them as independent diagnoses. The association between polytherapy and psychiatric disease indicates that psychiatric diseases are more likely to occur in severe epilepsy. Polytherapy could also have side effects, manifesting as psychiatric symptoms.

Depression was the self-reported psychiatric disorder most frequently associated with epilepsy, especially for untreated women prior to pregnancy. The discrepancy between self-reported depression and HSCL scores during pregnancy for the group with epilepsy indicates an underestimation of depression by the women themselves and that women with epilepsy are at risk of depression both during and prior to pregnancy. Mood disturbance and stress during pregnancy are associated with preterm birth or growth restriction in the fetus [46]. Women with epilepsy have an increased risk of gestational complications [29]. This adds to the importance of reducing depression and anxiety in pregnant women with epilepsy. The burden of epilepsy, affecting social functioning and leading to a reduced quality of life [18–23], is probably more important for depression and anxiety than the epileptic activity itself [19]. The incidence of depression, anxiety, and suicide attempts preceding epileptic seizures [12,13,47] indicates that psychiatric disorders may predispose individuals to epileptic activity. An association between epilepsy and psychosis in adults and children [10] supports the theory of a bidirectional relationship between epilepsy and psychiatric disorders [9,12,13,47].

Our study revealed an association between epilepsy and eating disorders prior to pregnancy. This finding is supported by a recent population-based study [6]. The burden of epilepsy, with fear of seizures, social stigma, and low self-esteem, is a plausible explanation. However, after adjusting for both socioeconomic and psychiatric factors, this relationship still persisted, indicating epilepsy as a specific risk factor. During pregnancy, eating disorders are uncommon apart from pregnancy-induced nausea, and we found no difference between women with and without epilepsy in pregnancy.

In contrast to previous studies, we did not find anxiety to be overrepresented in epilepsy. Our estimates reflect an anxiety frequency that is representative for young women with epilepsy who are otherwise healthy as we included all pregnant females in a population-based cohort.

Women with epilepsy reported more adverse social outcomes during pregnancy than those in the reference group, and this was most pronounced for the AED-treated group. This probably reflects that treated women, especially those undergoing polytherapy treatment, have more severe epilepsy. Epilepsy was associated with shorter education, which limits employment opportunities and income. Low income and unemployment due to disability were more frequent in our population with epilepsy.

We found an increased frequency of single parenting among the pregnant women with epilepsy. Unplanned pregnancy is more common among women with epilepsy [30], resulting in more women with epilepsy being single parents. Individuals with epilepsy are also less likely to get married [18,47,49]. Feelings of guilt and shame and concerns about epilepsy and seizures can interfere with the ability to form and keep close relationships [50]. Disability and unemployment can lead to loss of social connections and isolation. There were no differences between the group with epilepsy and the reference group concerning smoking, alcohol use, or use of narcotics prior to pregnancy. It is strongly recommended to avoid smoking and alcohol during gestation, and information on negative health effects and consequences for the child is widely given by the Norwegian health authorities. Accordingly, many women quit smoking and alcohol during pregnancy [25]. This is especially important in the group with epilepsy since epilepsy is associated with an increased risk for pregnancy complications and malformations in the child [32,51]. In contrast to former studies reporting lower alcohol use among persons with epilepsy, we found no such difference [18,25]. Better information regarding the ill effects of smoking probably explains the low frequency of smoking compared to former studies [25,48].

5. Conclusions

Epilepsy was associated with depression and eating disorders during and prior to pregnancy and also with adverse social aspects. The modest increase of psychiatric disorders in our study compared to previous reports may reflect improved treatment and follow-up during pregnancy, and young females before and during pregnancy should be in an optimal phase regarding lifestyle and general health. Also, women with epilepsy who get pregnant may be in better health than those who do not. The lower prevalence of psychiatric comorbidity may also reflect little or no selection bias in the cohort. Depression seems to be underdiagnosed, and both AED-treated and untreated women with epilepsy are at a particular risk of depression both prior to and during pregnancy. Antiepileptic drugs may stabilize psychiatric dysfunction. On the other hand, AED treatment, especially polytherapy, is associated with poor social function because of more severe and treatment-dependent epilepsy. Such risks should be accounted for in clinical follow-up and is of special importance before and during pregnancy. In the treatment of epilepsy, comorbidity of any psychiatric disorder should always be considered. This is necessary for deciding the optimal drug of choice, avoiding drug interactions, and minimizing side effects. Screening tools for depression, anxiety, and psychosomatic complaints are useful for young women with epilepsy.

Conflict of interest

Author G. Veiby has received travel support from UCB Pharma SA and lecture fees from GlaxoSmithKline. Author B. Engelsen has received travel support from GlaxoSmithKline and lecture fees from H. Lundbeck AS. The remaining authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2013.08.016.

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Supplemental material paper I

eTable 1. Social characteristics of women with epilepsy with and without use of antiepileptic drugs (AEDs) during pregnancy compared to the reference group.[1]

	Reference group (n = 89499)	Epilepsy all (n = 634, 0.7 %)			Epilepsy with AED (n = 291, 0.3 %)			Epilepsy without AED (n = 343, 0.4 %)		
Characteristics	**% (n)**	**% (n)**	**p-value**	**OR (CI)**	**% (n)**	**p-value**	**OR (CI)**	**% (n)**	**p-value**	**OR (CI)**
Mean age in years (SD)	29.5 (4.7)	29.0 (4.9)	0.01	NA	29.0 (4.9)	0.062	NA	29.0 (5.0)	0.064	NA
Low education (< 12 years)	33.5 (29993)	50.2 (318)	<0.001	**2.0** (1.7-2.3)	51.5 (150)	<0.001	**2.1** (1.7-2.7)	49.0 (168)	<0.001	**1.9** (1.5-2.4)
Low income	19.3 (15800)	25.1 (149)	<0.001	**1.4** (1.2-1.7)	28.6 (77)	<0.001	**1.7** (1.3-2.2)	22.2 (72)	0.18	**1.2** (0.9-1.6)
No income	2.7 (2219)	4.4 (26)	0.012	**1.6** (1.1-2.4)	5.2 (14)	0.01	**2.0** (1.2-3.4)	3.7 (12)	0.27	**1.4** (0.8-2.5)
Unemployed due to disability	1.6 (1464)	8.0 (51)	<0.001	**5.3** (3.9-7.0)	8.9 (26)	<0.001	**5.9** (3.9-8.9)	7.3 (25)	<0.001	**4.7** (3.1-7.1)
Single parenting	2.7 (2244)	4.8 (30)	<0.001	**1.9** (1.3-2.7)	4.6 (13)	0.042	**1.8** (1.0-3.1)	5.0 (17)	0.007	**1.9** (1.2-3.2)
Smoking during pregnancy	8.7 (7731)	10.4 (66)	0.13	**1.2** (0.9-1.6)	12.1 (35)	0.044	**1.4** (1.0-2.0)	9.1 (31)	0.82	**1.1** (0.7-1.5)
Alcohol during pregnancy	2.4 (2175)	3.2 (20)	0.24	**1.3** (0.8-2.0)	4.1 (12)	0.062	**1.7** (1.0-3.1)	2.3 (8)	0.91	**1.0** (0.5-1.9)
Narcotics prior to pregnancy	10.1 (9029)	10.7 (68)	0.60	**1.1** (0.8-1.4)	9.6 (28)	0.79	**0.9** (0.6-1.4)	11.7 (40)	0.33	**1.2** (0.8-1.6)

Unadjusted OR, odds ratio; CI, confidence interval; SD, standard deviation; NA, not applicable.

1. Only the first pregnancy during the recording period is included in the analyses, for both the epilepsy and reference groups.

eTable 2. Risk of low income, low education and unemployment in subgroups of AED treated women with epilepsy compared to the reference

	Low income [2] (n=16048, 17.7 %)			**Low education** [3] (n=30504, 33.6 %)			**Unemployment due to disability** (n=1527, 1.7 %)		
Group	**% (n)**	**p-value**	**OR (CI)**	**% (n)**	**p-value**	**OR (CI)**	**% (n)**	**p-value**	**OR (CI)**
Reference	19.3 (15800)	NA	1	33.5 (29993)	NA	1	1.6 (1464)	NA	1
Polytherapy	46.9 (23)	<0.001	**3.7** (2.1-6.5)	57.4 (31)	<0.001	**2.7** (1.6-4.6)	25.9 (14)	<0.001	**21.0** (11.4-38.8)
Valproate[4]	14.8 (4)	0.56	**0.7** (0.3-2.1)	40.6 (13)	0.39	**1.4** (0.7-2.7)	6.2 (2)	0.10	**4.0** (1.0-16.8)
Carbamazepine[4]	24.2 (15)	0.33	**1.3** (0.7-2.4)	55.6 (35)	<0.001	**2.5** (1.5-4.1)	3.2 (2)	0.28	**2.0** (0.5-8.1)
Lamotrigine[4]	28.2 (24)	0.036	**1.6** (1.0-2.6)	48.9 (44)	0.002	**1.9** (1.3-2.9)	6.7 (6)	0.004	**4.3** (1.9-9.8)

group.[1]

Unadjusted OR, odds ratio; CI, confidence interval; SD, standard deviation; NA, not applicable.

1. Only the first pregnancy during the recording period is included, for both the epilepsy and reference groups.
2. Annual income < 19,000 Euro.
3. Education of 12 years or less.
4. Monotherapy.

eTable 3. Self-reported depression, anxiety, and eating disorders before and during pregnancy. All epilepsy groups are compared to the reference group.[1]

	Before pregnancy			During pregnancy		
Group	**% (n)**	**p-value**	**OR (CI)**	**% (n)**	**p-value**	**OR (CI)**
Depression						
Reference	6.6 (5872)	NA	1	2.5 (2223)	NA	1
Epilepsy	9.3 (59)	0.005	1.5 (1.1-1.9)	2.4 (15)	0.9	1.0 (0.6-1.6)
AED	7.2 (21)	0.65	1.1 (0.7-1.7)	1.4 (4)	0.22	0.6 (0.2-1.5)
No AED	11.1 (38)	0.001	1.8 (1.3-2.5)	3.2 (11)	0.39	1.3 (0.7-2.4)
Anxiety						
Reference	3.6 (3190)	NA	1	1.5 (1380)	NA	1
Epilepsy	4.9 (31)	0.073	1.4 (1.0-2.0)	1.4 (9)	0.80	0.9 (0.5-1.8)
AED	3.4 (10)	0.91	1.0 (0.5-1.8)	1.0 (3)	0.64	0.7 (0.2-2.1)
No AED	6.1 (21)	0.011	1.8 (1.1-2.7)	1.7 (6)	0.76	1.1 (0.5-2.6)
Eating disorders[2]						
Reference	3.0 (2712)	NA	1	0.3 (312)	NA	1
Epilepsy	4.6 (29)	0.02	1.5 (1.1-2.2)	0.5 (3)	0.49	1.4 (0.4-4.2)
AED	2.7 (8)	0.78	0.9 (0.5-1.8)	0.0 (0)	NA	NA
No AED	6.1 (21)	0.001	2.1 (1.3-3.3)	0.9 (3)	0.12	2.5 (0.8-7.9)

Unadjusted OR, odds ratio; CI, confidence interval; SD, standard deviation; NA, not applicable.

1. Only the first recorded pregnancy is included in the analyses, for both the epilepsy and reference groups.
2. Anorexia nervosa, bulimia, or other eating disorder.

eTable 4. Depression as indicated by Hopkins Symptom Check List[1] and Lifetime Major Depression scores among pregnant women with epilepsy compared to the reference group without epilepsy.[1]

	Depression during pregnancy [2]			Earlier Major Depression		
Group	**% (n)**	**p-value**	**OR (CI)**	**% (n)**	**p-value**	**OR (CI)**
Reference	11.4 (9434)	NA	1	5.7 (4716)	NA	1
Epilepsy	17.2 (104)	< 0.001	1.6 (1.3-2.0)	7.4 (45)	0.061	1.3 (1.0-1.8)
AED	20.2 (55)	< 0.001	2.0 (1.5-2.6)	9.6 (26)	0.005	1.8 (1.2-2.7)
No AED	14.7 (49)	0.062	1.3 (1.0-1.8)	5.7 (19)	0.98	1.0 (0.6-1.6)
Polytherapy	23.1 (12)	0.008	2.3 (1.2-4.4)	11.8 (6)	0.067	2.2 (0.9-5.2)
Valproate[4]	20.7 (6)	0.14	2.0 (0.8-5.0)	7.1 (2)	0.67	1.3 (0.3-5.4)
Lamotrigine[4]	17.9 (15)	0.063	1.7 (1.0-3.0)	11.5 (10)	0.032	2.2 (1.1-4.2)
Carbamazepine[4]	18.6 (11)	0.081	1.8 (0.9-3.4)	6.8 (4)	0.58	1.2 (0.4-3.3)

Unadjusted OR, odds ratio; CI, confidence interval; SD, standard deviation; NA, not applicable.

1. Only the first pregnancy during the recording period is included in the analyses, for both the epilepsy and reference groups.
2. Hopkins Symptom Checklist, pregnancy weeks 13-17.
3. Lifetime Major Depression Scale.
4. Monotherapy

Paper II

II

PLOS ONE

RESEARCH ARTICLE

Psychiatric Comorbidity, Social Aspects and Quality of Life in a Population-Based Cohort of Expecting Fathers with Epilepsy

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Abstract

Objectives

To investigate psychiatric disorders, adverse social aspects and quality of life in men with epilepsy during partner's pregnancy.

Method

We used data from the Norwegian Mother and Child Cohort Study, including 76,335 men with pregnant partners. Men with epilepsy were compared to men without epilepsy, and to men with non-neurological chronic diseases.

Results

Expecting fathers in 658 pregnancies (mean age 31.8 years) reported a history of epilepsy, 36.9% using antiepileptic drugs (AEDs) at the onset of pregnancy. Symptoms of anxiety or depression were increased in epilepsy (7.0% and 3.9%, respectively) vs. non-epilepsy (4.6% and 2.5%, respectively, $p = 0.004$ and 0.023), and so were new onset symptoms of depression (2.0% vs. 1.0%, $p < 0.031$) and anxiety (4.3% vs. 2.3%, $p = 0.023$). Low self-esteem (2.5%) and low satisfaction with life (1.7%) were more frequent among fathers with epilepsy compared to fathers without epilepsy (1.3% and 0.7%, respectively, $p = 0.01$ and 0.010). Adverse social aspects and life events were associated with epilepsy vs. both reference groups. Self-reported diagnoses of ADHD (2.2%) and bipolar disorder (1.8%) were more common in epilepsy vs. non-epilepsy (0.4% and 0.3%, respectively, $p = 0.002$ and 0.003) and non-neurological chronic disorders (0.5% and 0.5%, respectively, $p = 0.004$ and 0.018). A screening tool for ADHD symptoms revealed a higher rate compared to self-reported ADHD (9.5% vs. 2.2%, $p < 0.001$).

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Conclusion

Expecting fathers with epilepsy are at high risk of depression and anxiety, adverse socio-economic aspects, low self-esteem, and low satisfaction with life. Focus on mental health in fathers with epilepsy during and after pregnancy is important. The use of screening tools can be particularly useful to identify those at risk.

Introduction

Pregnancy and birth generally have a positive impact on the parent's life and well-being, but may also be associated with increased stress, anxiety, and other forms of psychiatric dysfunction. Early recognition of emotional distress in women during pregnancy and the post-partum period is important in order to prevent complications such as birth-anxiety and post-partum depression [1]. Expecting fathers are increasingly involved during and after pregnancy and studies suggest that they too may be predisposed to psychiatric dysfunction, including anxiety and depression during pregnancy and post-partum, as well as a general decline in mental health during the first year after birth [2–4]. Moreover, studies show that lack of support from the partner is a risk factor for emotional dysfunction in both parents [3] and this effect is stronger in the presence of pre-existing somatic or mental illness [5, 6].

Both men and women with epilepsy have an increased risk of psychiatric comorbidity, including depression and anxiety [7, 8]. Epilepsy has also been linked to ignorance and superstition, causing fear and stigma, with a negative impact on aspects such as education, employment, intimate relationships, and quality of life [9, 10]. This burden can add to a vulnerable situation for both fathers and mothers with epilepsy during pregnancy. Women with epilepsy face extra challenges related to antiepileptic drug (AED) -treatment in order to maintain seizure control during and after gestation [11]. They are also at higher risk of peri-partum depression or anxiety than women without epilepsy [12]. Although men are not physiologically influenced by childbearing, mental health during and after pregnancy can be affected by psychological factors such as insecurity about seizures and the new challenges of fatherhood. Our hypothesis is that the increased risk of psychosocial challenges in persons with epilepsy may add to a vulnerable situation during pregnancy for expecting fathers. This can be examined by our unique dataset, from which we have conducted a cross-sectional study based on a large national cohort of men with detailed self-reported data during their partner's pregnancy.

Material and Methods

Data collection and assessment of diagnoses

This cross-sectional study included data from version 5 of the quality-assured data files based on The Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health[13]. A detailed description of the cohort has been published previously [13]. From the year 2000 the mothers' partners were invited to participate, and 87% of the expecting fathers agreed to participate. The present study included all 76,335 pregnancies with data from the expecting fathers during gestational weeks 13–17, with detailed information on past and current psychiatric diseases, socioeconomic conditions, and AED use during the last six months prior to pregnancy.

The main control group to be included was expecting fathers without epilepsy. An additional group with non-neurological chronic disorders was chosen to assess whether

associations found for epilepsy were epilepsy-specific rather than caused by the burden of a chronic disorder in general. The stratification into AED treated and untreated epilepsy is relevant as a marker for epilepsy severity and potential AED effects. AEDs could modulate psychiatric symptoms.

Fathers with epilepsy (FWE) comprised 658 unique pregnancies, and were classified according to AED use during the last 6 months (yes/no), and further divided into four main AED groups: Monotherapies with valproate (VPA, n = 59), carbamazepine (CBZ, n = 91), or lamotrigine (LTG, n = 40), and multiple AEDs (polytherapy, n = 30). The total epilepsy group were compared to a reference group of all fathers in MoBa without epilepsy (n = 75,677). A subgroup of 8,475 of the references had a non-neurological chronic disorder (NNCD), including diabetes, rheumatic arthritis, heart disease or asthma. This group served as a second reference group.

Variables

The screening instruments were constructed as dichotomous variables. The instruments and measures are presented in S1 Table. Current depressive and anxiety symptoms were measured separately by a short version of the Hopkins' Symptom Check List [14] with 4-items scales for depression (SCL-D) and anxiety (SCL-A). A mean score > 1.75 was set as cut off for significant depression or anxiety [14]. Previous depression was assessed by the Life Time Major Depression Scale (LTMD, S1 Table), a validated tool [15] which meets DSM III-criteria for lifetime major depression when i) at least three types of symptom items are endorsed, ii) one of these symptoms is the first (felt depressed), iii) three types of symptoms occurred simultaneously. Screening-positive ADHD symptoms were assessed by a 6-item short version of the Adult ADHD Self Report Scale (ASRS). ASRS has shown good internal consistency for use in both epidemiological and clinical surveys [16] (S1 Table). Quality of life was evaluated through the 4-item short version of Rosenberg's Self Esteem Scale (RSES) and 5-item Satisfaction With Life Scale (SWLS) (S1 Table). The short version of RSES has shown a 0.95 correlation with the original 10 items scale [17, 18], and SWLS has also been validated as robust [19]. Low satisfaction with life was defined as SWLS score ≤ 9. Cronbach's alpha was 0.81 for LTMD, 0.69 for SCL-D, 0.78 for SCL-A, 0.50 for ASRS, 0.71 for RSES and 0.86 for SWLS. A maximum likelihood estimation procedure for missing values was applied for the screening tools to avoid potential sample distortions [20]. Screening outcomes with $\geq$ 20% missing data were excluded from the analyses. Predefined psychiatric diagnoses in the questionnaire included: Attention Deficit Hyperactivity Disorder (ADHD) (yes/no), bipolar disorder (yes/no) anorexia/bulimia/other eating disorder (ED) (yes/no), and schizophrenia (yes/no). In addition the questionnaire included a box for unspecified (other) psychiatric disorders (yes/no). Paternal demographic and socioeconomic variables included age (years), low educational level ($\leq$ 12 years), low income ($\leq$ 26,704 Euro/year), unemployment due to disability (yes/no), current smoking (yes/no), high alcohol use during partner's pregnancy ($>$ ten units/week), and a history of narcotic use (yes/no). Narcotics included cannabis, amphetamine, ecstasy, cocaine, and heroin. Amphetamine recorded as a narcotic was assessed through specific questions on drug abuse separate from questions on use of medication in relation to ADHD. Low income was defined according to The European Commission, including a household income per consumption unit $<$ 60 percent of the median [21, 22]. Financial insecurity was defined as not being able to handle unexpected expenses of 1,180 Euro in a month. 11 adverse life events were assessed by the question "Have you experienced any of the following (events) during the past 12 months?" (S1 Table) (yes/no).

During the MoBa inclusion period the questionnaires were modified several times, resulting in some of the variables being available only from later questionnaire versions (D and E), and numbers are lower for these analysis.

Statistics

SPSS Statistics 21.0 (SPSS Inc., Chicago, IL, USA) was used to perform the analyses. Mean age was compared through independent-samples t-test. All other measures were constructed as dichotomous variables and were analyzed by Pearson's chi-square test, and by Fisher's exact test for cross-tabulations with expected cell count less than five. Results are presented as crude frequencies and unadjusted odds ratios (OR) with 95% confidence interval (CI) and corresponding p-values. Two-sided p-values < 0.05 were considered statistically significant. When significant differences were found between the epilepsy group and control groups through chi square testing, the differences were further tested with binary logistic regression analysis for potential classical confounders as well as socioeconomic conditions associated with epilepsy in our analysis. Results are presented with adjusted OR with 95% CI and corresponding p-values. OR, CI and p-values in all tables and figures refer to comparisons between the fathers with epilepsy and the main reference group without epilepsy. Significant differences between the epilepsy and NNCD groups are marked with "#" in the tables and figures. Age, low income, and low educational level were considered potential confounders. McNemar test was used to compare differences between dichotomous variables for diagnoses vs. symptoms.

Ethics

The MoBa study and the current sub study have been approved by The Regional Committee for Medical Research Ethics in Western Norway (2010/788).

Results

0.9% (n = 658) of the expecting fathers reported a history of epilepsy (Table 1), 36.9% (n = 243) having used AEDs during the last six months prior to partners pregnancy, the majority as AED monotherapy (87.2%, n = 212).

Psychiatric symptoms and self-reported disease

During pregnancy, FWE more frequently reported symptoms consistent with anxiety (SCL-A) and depression (SCL-D) compared to the reference group, but not more frequently than fathers with NNCD (Fig 1). The association between epilepsy and anxiety was consistent after adjustment for confounders (OR = 1.7, p = 0.018), but not for depression (OR = 1.6, p = 0.13) (complete list of adjusted numbers for symptoms in S2 Table). Significantly more FWE had new onset symptoms of depression (2.0% vs. 1.0%, OR = 1.8, CI = 1.0–3.2, $p < 0.031$) and anxiety (4.3% vs. 2.3%, OR = 1.8, CI = 1.3 p = 0.023) during pregnancy compared to the references without epilepsy. Previous depression was more common in the AED-treated group (Fig 1). This association was not consistent after adjustment for confounders (S2 Table). Expecting fathers with a history of previous depression more often reported anxiety (21.8% vs. 2.7%, OR = 10.2, CI = 9.5–10.9, $p < 0.001$) or depression (13.7% vs. 1.3%, OR = 12.6, CI = 11.5–13.8, $p < 0.001$) during pregnancy compared to those without previous depression, and with no significant difference between fathers with and without epilepsy. Anxiety/depression did not differ in FWE who reported expecting their first child vs. FWE with children from before.

ADHD was the second most common screening-positive diagnosis after previous depression among all the expecting fathers (Fig 1 and S2 Table). No difference in prevalence was found between men with and without epilepsy, or between FWE and fathers with NNCD. Screening-positive ADHD showed a higher prevalence than self-reported ADHD in men both with and without epilepsy (Fig 2). For FWE 2.2% reported ADHD while 9.5% had a positive symptom score for ADHD ($p < 0.001$).

Table 1. Percentage and number (n) of individuals with various social characteristics in fathers with epilepsy with and without use of antiepileptic drugs (AEDs) compared to a reference group without epilepsy. Fathers with non-neurological chronic disorders (NNCD) served as an additional internal control group.

	References (n = 75677)	NNCD (n = 8475, 11.1%)	Epilepsy all (n = 658, 0.9%)			Epilepsy with AED (n = 243, 0.3%)			Epilepsy without AED (n = 415, 0.5%)		
Characteristics	**% (n)**	**% (n)**	**% (n)**	**p-Value**	**OR (CI)**	**% (n)**	**p-Value**	**OR (CI)**	**% (n)**	**p-Value**	**OR (CI)**
Mean age in years (SD)	32,3 (5.4)	32.1 (5.3)##	31.8 (5.6)	0.009	NA	32.1 (5.4)	0.14	NA	31.7 (5.7)	0.031	NA
Low education (< 12 years)	46.7 (35357)	49.3 (4144)	48.9 (322)	0.26	**1.1** (0.9–1.3)	48.1 (117)	0.66	**1.1** (0.8–1.4)	49.4 (205)	0.28	**1.1** (0.9–1.4)
Low income[1]	5.4 (1776)	5.9 (229)##	9.9 (27)	0.001	**1.9** (1.3–2.9)	10.3 (10)	0.031	**2.0** (1.1–3.9)	9.7 (17)	0.011	**1.9** (1.1–3.1)
Lack of financial security[1]	18.4 (6069)	20.8 (801)	22.5 (61)	0.079	**1.3** (1.0–1.7)	21.9 (21)	0.37	**1.2** (0.8–2.0)	22.9 (40)	0.13	**1.3** (0.9–1.9)
Unemployed due to disability	1.4 (1043)	2.8 (239)##	5.2 (34)	<0.001	**3.9** (2.7–5.5)	9.1 (22)	<0.001	**7.1** (4.5–11.0)	2.9 (12)	0.009	**2.1** (1.2–3.7)
Sick leave > 8 weeks[1]	6.2 (1244)	8.7 (215)	11.2 (21)	0.005	**1.9** (1.2–3.0)	15.3 (11)	0.005	**2.7** (1.4–5.2)	8.7 (10)	0.27	**1.4** (0.75–2.8)
Smoking	23.6 (17858)	24.6 (2065)	24.3 (160)	0.67	**1.0** (0.9–1.2)	19.3 (47)	0.12	**0.8** (0.6–1.1)	27.2 (113)	0.082	**1.2** (1.0–1.5)
Alcohol[1]	4.8 (1626)	5.4 (213)	5.4 (15)	0.65	**1.1** (0.7–1.9)	5.1 (5)	0.81	**1.0** (0.4–2.6)	5.6 (10)	0.63	**1.2** (0.6–2.2)
Narcotics ever	17.2 (13033)	19.4 (1634)	17.6 (116)	0.78	**1.0** (0.8–1.3)	12.3 (30)	0.044	**0.7** (0.5–1.0)	20.7 (86)	0.060	**1.3** (1.0–1.6)

Significant difference between the NNCD versus 'Epilepsy all' groups:

##p < 0.01.

Unadjusted OR, odds ratio; CI, confidence interval; SD, standard deviation; NA, not applicable.

[1]. Data from questionnaire version D and E only.

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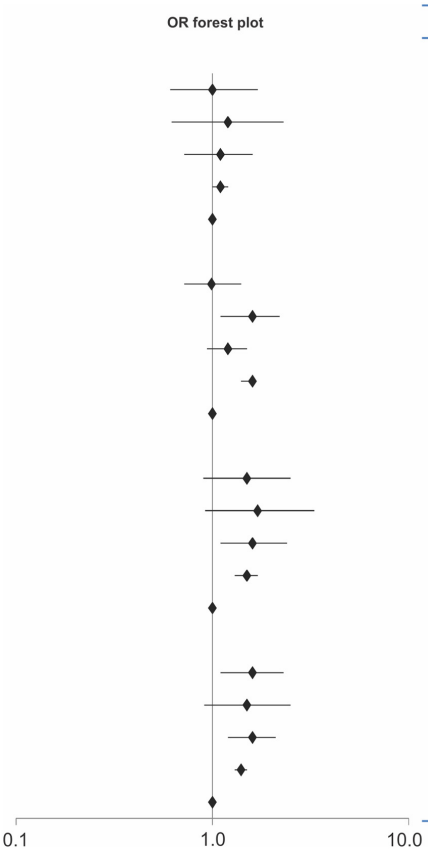
A self-reported diagnosis of psychiatric disease was more frequent among FWE compared to the reference group (6.9% vs. 3.1%, p < 0.001), but not compared to those with NNCD (6.9% vs. 4.5%, p = 0.076). Psychiatric diagnoses were most common in AED-untreated epilepsy (Fig 3), 9.0% of AED-untreated (p < 0.001) and 3.0% of AED treated men (p = 1.00). ADHD was the most common self-reported psychiatric disorder, and both ADHD and bipolar disorder were increased in FWE compared to both reference groups (Fig 3). After adjustment for confounders, the OR of reporting ADHD was 3.2 in all FWE (p = 0.014) and 5.1 in the untreated group (p = 0.001), and OR for bipolar disorder was 4.1 in all FWE (p = 0.007) and 4.9 in the untreated group (p = 0.008) compared to the references (complete list of adjusted frequency for diagnoses in S3 Table). Other, unspecified psychiatric disorders were also more common among FWE compared to the references. In the untreated FWE we found OR = 2.6 (p = 0.004) after adjustment for confounders. No difference was found between FWE and the NNCD group.

Self-esteem and satisfaction with life

Low self-esteem and low satisfaction with life were more common among FWE (Table 2). After adjustment for confounders, the association for low satisfaction with life remained significant (Table 2).

Social characteristics and adverse life events

FWE reported a higher frequency of adverse social characteristics compared to the non-epilepsy reference group (Table 1). Low income, unemployment due to disability, and financial



Group	OR (CI)	p-Value	Frequency % (n)
ASRS (ADHD)			
No AED	**1.0** (0.61-1.7)	0.94	9.0 (16)
AED	**1.2** (0.62-2.3)	0.60	10.4 (10)
Epilepsy	**1.1** (0.72-1.6)	0.71	9.5 (26)
NNCD	**1.1** (1.0-1.2)	¤	9.5 (370)
Reference	1.0		8.9 (2948)
LTMD (previous depression)			
No AED	**0.99** (0.72-1.4)	0.96	10.0 (41)
AED	**1.6** (1.1-2.2)	0.012	15.0 (36)
Epilepsy	**1.2** (0.94-1.5)	0.14	11.9 (77)
NNCD	**1.5** (1.4-1.6)	¤	13.8 (1148)
Reference	1.0		10.1 (7561)
SCL_D (current depression)			
No AED	**1.5** (0.90-2.5)	0.12	3.7 (15)
AED	**1.7** (0.92-3.3)	0.088	4.2 (10)
Epilepsy	**1.6** (1.1-2.4)	0.023	3.9 (25)
NNCD	**1.5** (1.3-1.7)	¤	3.5 (292)
Reference	1.0		2.5 (1853)
SCL_A (current anxiety)			
No AED	**1.6** (1.1-2.3)	0.014	7.1 (29)
AED	**1.5** (0.91-2.5)	0.11	6.7 (16)
Epilepsy	**1.6** (1.2-2.1)	0.004	7.0 (45)
NNCD	**1.4** (1.3-1.6)	¤	6.2 (512)
Reference	1.0		4.6 (3422)

Fig 1. Frequencies for symptoms of ADHD tested with ASRS, previous depression tested with LTMD, current depression tested with SCL_D and current anxiety tested with SCL_A in fathers with epilepsy with and without use of antiepileptic drugs (AEDs) compared to a reference group without epilepsy. Unadjusted p-values and odds ratios (OR) are given for these comparisons. Fathers with non-neurological chronic disorders (NNCD) served as an additional internal control group. ¤ No significant difference between the NNCD versus 'Epilepsy all' groups. CI, confidence interval; SD, standard deviation; ASRS, Adult ADHD Self Report Scale; LTMD, Lifetime Major Depression Scale; SCL_D, Hopkins Symptom Check List for current depressive symptoms; SCL_A, Hopkins Symptom Check List for current anxiety symptoms.

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problems were more common among FWE compared to the references without epilepsy, and to NNCD (Table 1). The proportion of FWE reporting sick leave for more than 8 weeks yearly was higher than in men without epilepsy, but not compared to NNCD.

Adverse life events such as serious illness, having experienced physical violence, financial problems and conflict with family/friends/neighbors during the last 12 months, was more common among FWE compared to the reference group without epilepsy and the NNCD group (Table 3).

Polytherapy and monotherapy

Complete crude frequencies with unadjusted OR and p-values for diagnoses and screening tools in the polytherapy and three monotherapy groups are found in S4 Table. Most

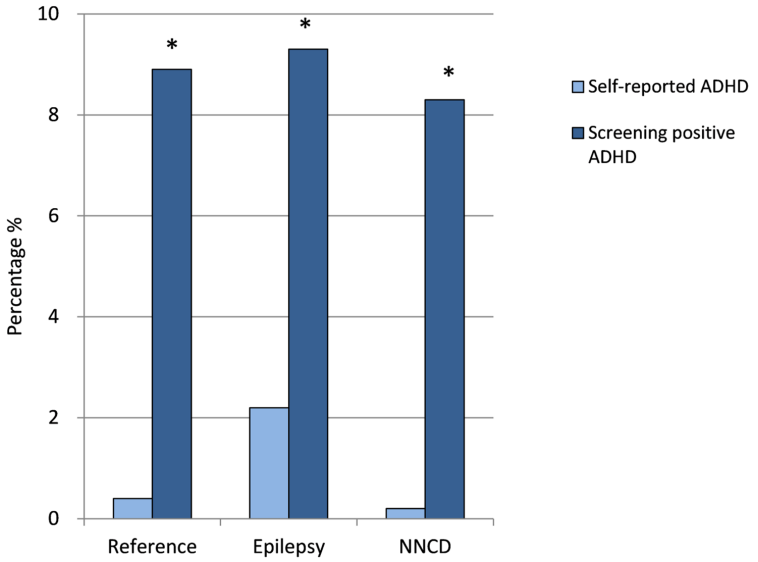

Fig 2. Self-reported diagnosis of ADHD vs. screening positive for ADHD symptoms in the epilepsy group, the reference group without epilepsy, and the group with non-neurological chronic disorders (NNCD). *Level of significance < 0.001.

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observations were too rare to give significant numbers. In polytherapy-treated FWE there was one observation of bipolar disorder (7.7%, OR = 25.4, p = 0.042). In the VPA group six fathers reported anxiety (10.3%, OR = 2.4, p = 0.049) and three reported low satisfaction with life (5.2%, OR = 7.4, p = 0.009).

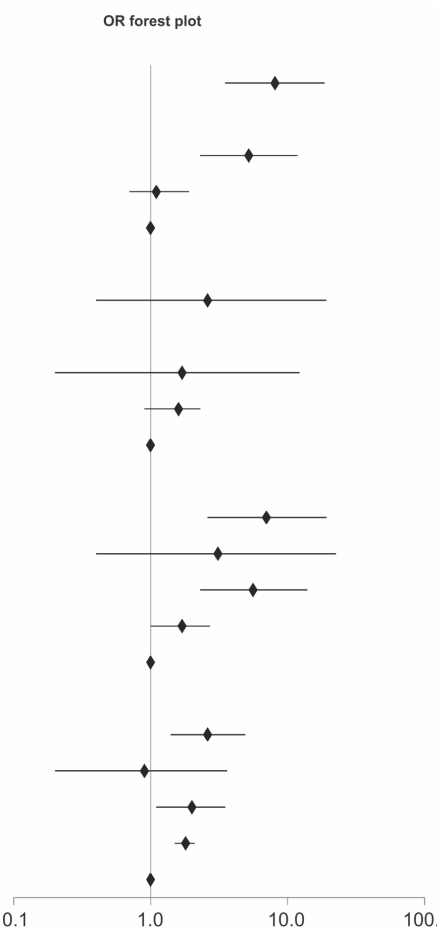
Discussion

Key findings

FWE more often had symptoms of anxiety and depression during pregnancy compared to both men without epilepsy and to men with other chronic disorders. The risk-estimates of psychiatric symptoms were similar for AED treated and untreated epilepsy groups. FWE also had an increased risk of ADHD, bipolar disorder, and other psychiatric disorders compared to both reference groups. Low self-esteem and low satisfaction with life was associated with epilepsy, as were adverse social aspects and life events.

Strengths and limitations

This is the first study to compare mental health and socioeconomic conditions between expecting fathers with and without epilepsy. The cohort was collected from the general population and included both AED-treated and untreated epilepsy, reducing the risk of selection bias commonly associated with institutional-based cohorts. The reference group represents a large and heterogeneous population, leading to risk estimates that are more clinically applicable than in studies including only healthy controls. The data on socioeconomic aspects, and the broad spectrum of disorders recorded in MoBa, provides the possibility to adjust for confounders,



Group	OR (CI)	P-value	Frequency % (n)
ADHD			
No AED	**8.1** (3.5-18.6)	<0.001	3.4 (6)
AED	NA	NA	0.0 (0)
Epilepsy	**5.2** (2.3-11.8)	0.002	2.2 (6)
NNCD	**1.1** (0.70-1.9)	##	0.5 (18)
Reference	1.0		0.4 (144)
Eating disorders			
No AED	**2.6** (0.4-19.1)	0.32	0.6 (1)
AED	NA	NA	0.0 (0)
Epilepsy	**1.7** (0.2-12.2)	0.45	0.4 (1)
NNCD	**1.6** (0.86-3.0)	¤	0.3 (12)
Reference	1.0		0.2 (72)
Bipolar disorder			
No AED	**7.0** (2.6-19.2)	0.003	2.2 (4)
AED	**3.1** (0.4-22.5)	0.28	1.0 (1)
Epilepsy	**5.6** (2.3-13.9)	0.003	1.8 (5)
NNCD	**1.7** (1.0-2.7)	#	0.5 (19)
Reference	1.0		0.3 (110)
Unspecified psychiatric disorder			
No AED	**2.6** (1.4-4.9)	0.008	5.6 (10)
AED	**0.9** (0.2-3.6)	1.00	2.0 (2)
Epilepsy	**2.0** (1.1-3.5)	0.022	4.3 (12)
NNCD	**1.8** (1.5-2.1)	¤	3.5 (138)
Reference	1.0		2.3 (763)

Fig 3. Frequencies for self-reported diagnoses of ADHD, eating disorders, bipolar disorder and other (unspecified) psychiatric disorders in fathers with epilepsy with and without use of antiepileptic drugs (AEDs) compared to a reference group without epilepsy. Unadjusted p-values and odds ratio (OR) are given for these comparisons. Fathers with non-neurological chronic disorders (NNCD) served as an additional internal control group. Significant difference between the NNCD versus 'Epilepsy all' groups: #p < 0.05; ##p < 0.01. ¤ No significant difference between the NNCD versus 'Epilepsy all' groups. CI, confidence interval; NA, not applicable.

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and to compare epilepsy with other chronic disorders. Only 36.9% of the expecting fathers with epilepsy reported being treated with AED. This illustrates that most of them do not have active epilepsy with high risk of new seizures, but rather a history of previous epilepsy. This history is regarded as so relevant for their present health that they report it as a diagnosis. The fraction of individuals with a history of epilepsy using AED at present is in line with reports from other population-based registry studies [23, 24], which also demonstrated that AED treatment increases with increasing age. The mean age in our study population was 32 years. A near 100% validity for both the epilepsy diagnosis and use of medication has been shown for

Table 2. Percentage and number (n) of individuals with low self-esteem and low satisfaction with life among fathers with epilepsy with and without use of antiepileptic drugs (AEDs) compared to a reference group without epilepsy. Fathers with non-neurological chronic disorders (NNCD) served as an additional internal control group.

Group	% (n)	Unadjusted p-Value	OR (CI)	Adjusted p-Value	OR (CI)
Low Self Esteem					
References	1.3 (980)				
NNCD	1.8 (145)	¤	-	-	-
Epilepsy	2.5 (16)	0.011	**1.9** (1.2–3.1)	0.083	**1.6** (0.94–2.6)
AED	2.5 (6)	0.14	**1.9** (0.85–4.3)	0.47	**1.4** (0.59–3.1)
No AED	2.5 (10)	0.045	**1.9** (1.0–3.5)	0.093	**1.7** (0.91–3.3.)
Low Satisfaction With Life					
References	0.7 (549)				
NNCD	1.0 (84)	¤	-	-	-
Epilepsy	1.7 (11)	0.010	**2.3** (1.3–4.3)	0.021	**2.1** (1.1–3.8)
AED	2.5 (6)	0.009	**3.5** (1.5–7.9)	0.018	**2.7** (1.2–6.2)
No AED	1.2 (5)	0.23	**1.6** (0.69–4.1)	0.31	**1.6** (0.65–3.9)

¤ No significant difference between the NNCD versus 'Epilepsy all' groups.

OR, unadjusted odds ratio; CI, confidence interval.

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women with AED treated epilepsy in MoBa. Patients not treated with AEDs generally had inactive epilepsy [25]. Also, the prevalence of epilepsy is within the expected range for Western countries for both women and men in MoBa [26, 27]. The MoBa participation rate of 40.6% is as expected for large-scale population based cohorts [28]. Systematic bias caused by non-participants could be a concern, and a validation study on women in MoBa showed that they were slightly biased towards more favorable socioeconomic factors [29]. However, the same study found that exposure-outcome-rates were not affected by non-respondents or self-selection. Thus, comparisons between FWE and the reference groups are considered to be valid. The reported psychiatric diagnoses have not been validated, but complete versions of all screening tools applied have been validated.

A limitation of the present study is the lack of follow-up of the fathers post-partum. Post-partum health information would have been valuable to assess the specific effect of pregnancy. Information on type of epilepsy and seizure frequency would have determined epilepsy-specific effects in more detail.

Interpretations

Depression and anxiety were more common in FWE compared to fathers without epilepsy. New onset of such symptoms during partner's pregnancy was also more common in FWE, indicating that pregnancy constitutes a particular risk for mental health in epilepsy. Depression is the psychiatric disorder most commonly associated with epilepsy [30], and the association between epilepsy and anxiety is stronger than for other chronic disorders [31]. Newer studies suggest that expecting fathers are at risk of experiencing peri-partum depression and anxiety in relation to birth and life changes [2–4]. In fathers with epilepsy this may add to the burden of living with a chronic disorder. During childhood, restrictions and overprotection can cause stigma [8, 32]. Social insecurity and anxiety can affect friendships and social networks, the chance to find a life partner, choice of education, and work possibilities. Low income and lack of financial security were common in FWE, and both factors were associated with depression and anxiety. Private economic budgets become tighter with a new child, and this could worsen

Table 3. Percentage and number (n) of individuals with various adverse life events in fathers with epilepsy with and without use of antiepileptic drugs (AEDs) compared to a reference group without epilepsy. Fathers with non-neurological chronic disorders (NNCD) served as an additional internal control group.

	References (n = 33944) [1]	NNCD (n = 3959, 11.7%)[1]	Epilepsy all (n = 277, 0.8%)[1]			Epilepsy with AED (n = 99, 0.3%)[1]			Epilepsy without AED (n = 178, 0.5%)[1]		
Life events[1]	**% (n)**	**% (n)**	**% (n)**	**p-Value**	**OR (CI)**	**% (n)**	**p-Value**	**OR (CI)**	**% (n)**	**p-Value**	**OR (CI)**
Problems at work	27.7 (9222)	31.3 (1218)	30.0 (82)	0.39	**1.1** (0.86–1.5)	33.0(32)	0.25	**1.3** (0.84–2.0)	28.4 (50)	0.84	**1.0** (0.75–1.4)
Financial problems	15.1 (5040)	19.1 (746)[#]	25.2 (69)	<0.001	**1.9** (1.4–2.5)	26.8 (26)	0.001	**2.1** (1.3–3.2)	24.3 (43)	0.001	**1.8** (1.3–2.5)
Divorce/ separation	2.1 (712)	2.5 (99)	2.6 (7)	0.64	**1.2** (0.57–2.6)	0.00 (0)	NA	NA	4.0 (7)	0.11	**1.9** (0.88–1.0)
Personal conflicts	16.7 (5563)	19.6 (762)[#]	24.9 (68)	<0.001	**1.7** (1.3–2.2)	29.9 (29)	0.001	**2.1** (1.4–3.3)	22.2 (39)	0.053	**1.4** (0.99–2.0)
Concerns about baby	10.3 (3433)	11.5 (450)	12.8 (35)	0.19	**1.3** (1.0–1.8)	13.4 (13)	.032	**1.3** (0.75–2.4)	12.5 (22)	0.34	**1.2** (0.79–1.9)
Serious injury/illness	4.3 (1438)	8.2 (321)	11.0 (30)	<0.001	**2.7** (1.8–3.9)	18.6 (18)	<0.001	**5.0** (3.0–8.4)	6.9 (12)	0.10	**1.6** (0.91–2.9)
Close relative injured/ill	17.8 (5936)	21.4 (834)	19.3 (53)	0.52	**1.1** (0.82–1.5)	15.5 (15)	0.53	**0.84** (0.49–1.5)	21.5 (38)	0.21	**1.3** (0.88–1.8)
Traffic accident/ fire/ robbery	1.8 (613)	2.3 (91)	2.6 (7)	0.38	**1.4** (0.66–3.0)	3.1 (3)	0.27	**1.7** (0.54–5.4)	2.3 (4)	0.57	**1.2** (0.46–3.3)
Lost someone close	11.5 (3828)	12.7 (497)	14.3 (39)	0.15	**1.3** (0.91–1.8)	11.3 (119	0.96	**1.0** (0.53–1.8)	15.9 (28)	0.067	**1.5** (0.97–2.2)
Forced to sexual activity	0.2 (80)	0.4 (16)	0.00 (0)	NA	NA	0.00 (0)	NA	NA	0.00 (0)	NA	NA
Exposed to physical violence	1.5 (488)	2.0 (77)	3.6 (10)	0.008	**2.5** (1.3–4.8)	1.0 (1)	1.000	**0.70** (0.097–5.0)	5.1 (9)	0.001	**3.6** (1.8–7.1)

Significant difference between the NNCD versus 'Epilepsy all' groups:

[#]$p < 0.05$.

OR, unadjusted odds ratio; CI, confidence interval; SD, standard deviation; NA, not applicable.

[1]. Data only from questionnaire version D and E.

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symptoms of anxiety and depression [33, 34]. Unemployment and long term sick leave, also more common in FWE, may lead to loss of social connections and isolation, causing depression, and anxiety. Psychic and emotional distress may decrease the probability of returning to work, causing a vicious circle. We found that previous depression was an indicator of both depression and anxiety during pregnancy. Former studies have found prenatal paternal depression to be predictive of postnatal depression [35, 36], and postnatal depression correlated with emotional and behavioral problems in the child [37]. As father's mental health is a protective factor against depression in both mother and child [5], detecting symptoms of mental distress in the father early in pregnancy is important. Use of screening tools for symptoms of depression and anxiety represents an easy intervention.

We found a rather moderate prevalence of psychiatric disorders compared to former studies on non-pregnant persons with epilepsy [30, 38]. A plausible explanation is that pregnancy

represents a stabilizing event, and that men with a pregnant partner represent a selection towards better health with less mental complaints. A partner may be both a test and a proof of qualities such as social skills and accepted behavior, and provides support for a chronic health condition [39]. The prevalence of psychiatric disorders reported in the present study may also reflect modern treatment and follow-up. Another explanation could theoretically be that psychiatric symptoms are interpreted as a consequence of the epilepsy manifestation, or as side-effects from AEDs [40], and therefore not reported as separate symptoms or diagnoses. Still, epilepsy in expecting fathers was associated with more adverse life events, psychiatric symptoms and self-reported psychiatric diagnoses. These results were in accordance with two previous surveys on pregnant women with epilepsy in MoBa [12, 27], where the women reported higher levels of depression, anxiety and adverse social circumstances. Although pregnancy is considered a positive experience, it can also trigger stress, anxiety and depression [35, 41], adding to an already increased vulnerability of psychiatric comorbidity in epilepsy [7].

Our study revealed an increase of self-reported ADHD in expecting FWE compared to the reference groups, and more specifically in the AED-untreated group. ADHD is reported with increased frequency in children with epilepsy [42], and a recent study claimed that ADHD symptoms occurred in nearly 20% of adult epilepsy [43]. The lower prevalence in our study probably reflects a more accurate prevalence in a population of otherwise healthy young men recruited from the general population. Furthermore, men with more severe psychiatric challenges may be less likely to have children. However, the rate of screening-positive ADHD symptoms was higher than the self-reported diagnose. The discrepancy between the rate of self-reported diagnosis and symptoms could indicate that ADHD is underestimated or undiagnosed. Alternatively, ASRS as a screening instrument may be too sensitive.

The correlation between bipolar disorder and epilepsy remained significant after logistic regression, indicating an independent association, supported by previous reports on increased frequency of bipolar disorder in epilepsy [44].

The risk of low self-esteem and low satisfaction with life were twice as high in FWE compared to the references without epilepsy, but not compared to NNCD. Depression, anxiety and perceived stigma are important predictors of quality of life and self-esteem [34]. Having a partner is, however, important for quality of life, feeling of security and self-confidence, and this could explain the overall high satisfaction among this group with a pregnant partner.

Low income, unemployment and long term sick leave were unfavorable aspects associated with epilepsy. Adverse life events, such as serious illness, physical violence, financial problems and conflicts with other people were also related to epilepsy and more common than in NNCD. Life style aspects such as smoking and drinking did not differ between men with and without epilepsy. Health authorities recommend avoiding tobacco and alcohol during pregnancy, and pregnant women tend to moderate their smoking, drinking and nutrition habits. This may influence their partner in a positive way, accounting for the similarities between the groups with and without epilepsy, this differing from former studies on epilepsy outside pregnancy [9].

Self-reported psychiatric disorders were more common in AED-untreated FWE. This is in line with our previous study on women in MoBa [27]. As AED treatment could indicate more severe epilepsy, our finding was interesting. Several AEDs are used in the treatment of psychiatric disorders [45]. Such drugs could have a modulating effect on psychiatric comorbidity in epilepsy.

Conclusions

Men with epilepsy are at higher risk of depression, anxiety and other psychiatric disorders in relation to partner's pregnancy compared to men without epilepsy. They have an increased risk also for ADHD and bipolar disorder compared to men with other chronic disorders.

Adverse socioeconomic status, low self-esteem, and low satisfaction with life are also more common. We suggest that expecting fathers with epilepsy should be given more attention early in pregnancy, in particular regarding symptoms of depression and anxiety. The follow-up and treatment of psychiatric comorbidity is not only relevant to the expecting fathers, but also to their family and babies. The use of screening tools to assess comorbidity in epilepsy may be particularly useful to identify those at risk, as psychiatric diagnoses appear to be underreported.

Supporting Information

S1 Table. Variables used for Life Time Major Depression (LTMD), short version of Hopkin's Symptom Checklist (HSCL), Adult ADHD Self Report Scale (ASRS), Rosenberg's Self-Esteem Scale (RSES), and Satisfaction With Life Scale (SWLS). 1. Response option 1–4: "Not bothered", "A little bothered", "Quite bothered", "Very bothered". 2. Response option 1–5: "Never", "Seldom", "Sometimes", "Often", "Very often". 3. Response option 1–4: "Strongly agree", "Agree", "Disagree", "Strongly disagree". 4. Response option 1–7: "Disagree completely", "Disagree", "Disagree somewhat", "Neither nor", "Agree somewhat", "Agree", "Agree completely".
(DOCX)

S2 Table. Frequencies for symptoms of ADHD tested with ASRS, previous depression tested with LTMD, current depression tested with SCL_D and current anxiety tested with SCL_A in fathers with epilepsy with and without use of antiepileptic drugs (AEDs) compared to a reference group without epilepsy. Unadjusted and adjusted p-values and odds ratios (OR) are given for these comparisons. Fathers with non-neurological chronic disorders (NNCD) served as an additional internal control group. ¤ No significant difference between the NNCD versus 'Epilepsy all' groups. CI, confidence interval; SD, standard deviation; ASRS, Adult ADHD Self Report Scale; LTMD, Lifetime Major Depression Scale; SCL_D, Hopkins Symptom Check List for current depressive symptoms; SCL_A, Hopkins Symptom Check List for current anxiety symptoms.
(DOCX)

S3 Table. Frequencies for self-reported diagnoses of ADHD, eating disorders, bipolar disorder and other (unspecified) psychiatric disorders in fathers with epilepsy with and without use of antiepileptic drugs (AEDs) compared to a reference group without epilepsy. Unadjusted and adjusted p-values and odds ratio (OR) are given for these comparisons. Fathers with non-neurological chronic disorders (NNCD) served as an additional internal control group. Significant difference between the NNCD versus 'Epilepsy all' groups: #$p < 0.05$; ##$p < 0.01$. ¤ No significant difference between the NNCD versus 'Epilepsy all' groups. CI, confidence interval; NA, not applicable.
(DOCX)

S4 Table. Frequency of psychiatric symptoms (ADHD tested with ASRS, previous depression tested with LTMD, current depression tested with SCL_D and current anxiety tested with SCL_A), psychiatric diagnoses (ADHD, eating disorder, bipolar, unspecified psychiatric disorders), low satisfaction with life (SWLS) and low self-esteem (RSES) in fathers with epilepsy treated with antiepileptic drug (AED) polytherapy or monotherapy, compared to a reference group without epilepsy. Unadjusted p-values and odds ratios (OR) are given for these comparisons. CI, confidence interval; SD, standard deviation; NA, not applicable; ASRS, Adult ADHD Self Report Scale; LTMD, Lifetime Major Depression Scale; SCL_D, Hopkins Symptom Check List for current depressive symptoms; SCL_A, Hopkins Symptom Check List

for current anxiety symptoms; SWLS, Satisfaction With Life Scale" defined as score ≤ 9; RSES, Rosenberg Self-esteem scale.
(DOCX)

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Author Contributions

Conceived and designed the experiments: SFR NEG. Performed the experiments: SFR. Analyzed the data: SFR GV MHB. Contributed reagents/materials/analysis tools: SFR GV MHB AKD. Wrote the paper: SFR GV MHB AKD BAE NEG.

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Supplemental material paper II

S1 Table. Variables used for Life Time Major Depression (LTMD), short version of Hopkin's Symptom Checklist (HSCL), Adult ADHD Self Report Scale (ASRS), Rosenberg´s Self-Esteem Scale (RSES), and Satisfaction With Life Scale (SWLS).

Variables	Response options
Life Time Major Depression	
Have you ever experienced the following for a period of 2 weeks or more?	
Felt depressed, sad	No/ Yes
Had problems with appetite or eaten too much	No/ Yes
Been bothered by lack of energy	No/ Yes
Blamed yourself and felt worthless	No/ Yes
Had problems with concentration or had problems making decisions	No/ Yes
Had at least 3 of the problems named above simultaneously	No/ Yes
Was there a particular reason for this?	No/ Yes
Hopkins Symptom Checklist	
Have you been bothered by any of the following during the past two weeks?	
Feeling fearful	4 (1-4)[1]
Nervousness or shakiness inside	4 (1-4) [1]
Feeling hopeless about the future	4 (1-4)[1]
Feeling blue	4 (1-4)[1]
Worrying too much about things	4 (1-4)[1]
Feeling everything is an effort	4 (1-4)[1]
Feeling tense or keyed up	4 (1-4)[1]
Suddenly scared for no reason	4 (1-4)[1]
Adult ADHD Self Report Scale	
Feeling of anxiety and restlessness in the last six months:	
How often do you have problems completing the final aspects of a task when the challenging part is already done?	5 (1-5)[2]
How often do you have problems putting things in the right order when you are involved in tasks that require organization?	5 (1-5)[2]
When you have a task which requires a great deal of careful preparation, how often do you avoid or put off starting it?	5 (1-5)[2]
How often do you have problems remembering appointments or duties?	5 (1-5)[2]
When you have to sit still for a long time, how often do you move your hands and feet in an agitated and restless way?	5 (1-5)[2]
How often do you feel hyperactive and obliged to do things, as if you are being driven by an machine?	5 (1-5)[2]
Rosenberg´s Self-Esteem Scale	
What kind of perception do you have of yourself?	
I have a positive attitude towards myself	4 (1-4)[3]
I feel really useless at times	4 (1-4)[3]
I feel that I don't have much to be proud of	4 (1-4)[3]
I feel that I'm a valuable person, on an equal footing with anyone else, at any rate	4 (1-4)[3]

Satisfaction With Life Scale	
Do you agree or disagree with the following statements?	
My life is largely what I wanted it to be	7 (1-7)[4]
My life is very good	7 (1-7)[4]
I am satisfied with my life	7 (1-7)[4]
To date, I have achieved what is important for me in my life	7 (1-7)[4]
If I could start all over, there is very little I would do differently	7 (1-7)[4]
Life events	
Have you experienced any of the following during the last 12 months?	
Problems at work	
Financial problems	No/ Yes
Divorce/separation	No/ Yes
Conflicts with family/friends/neighbours	No/ Yes
Concerns about the baby	No/ Yes
Serious personal injury/illness	No/ Yes
Close relative being injured/ill	No/ Yes
Involved in traffic accident/fire/robbery	No/ Yes
Lost someone close	No/ Yes
Forced into sexual activity,	No/ Yes
Exposed to physical violence.	No/ Yes

1. Response option 1-4: “Not bothered”, “A little bothered”, “Quite bothered”, “Very bothered”.
2. Response option 1-5: “Never”, “Seldom”, “Sometimes”, “Often”, “Very often”.
3. Response option 1-4: “Strongly agree”, “Agree”, “Disagree”, “Strongly disagree”.
4. Response option 1-7: “Disagree completely”, “Disagree”, “Disagree somewhat”, “Neither nor”, “Agree somewhat”, “Agree”, “Agree completely”.

S2 Table. Frequencies for symptoms of ADHD tested with ASRS, previous depression tested with LTMD, current depression tested with SCL_D and current anxiety tested with SCL_A in fathers with epilepsy with and without use of antiepileptic drugs (AEDs) compared to a reference group without epilepsy. Unadjusted and adjusted p-values and odds ratios (OR) are given for these comparisons. Fathers with non-neurological chronic disorders (NNCD) served as an additional internal control group.

	Frequency	Unadjusted		Adjusted	
Group	**% (n)**	**p-Value**	**OR (CI)**	**p-Value**	**OR (CI)**
ASRS (ADHD)					
No AED	9.0 (16)	0.94	**1.0** (0.61-1.7)	0.73	**0.91** (0.53-1.6)
AED	10.4 (10)	0.60	**1.2** (0.62-2.3)	0.68	**1.2** (0.59-2.2)
Epilepsy	9.5 (26)	0.71	**1.1** (0.72-1.6)	0.97	**0.99** (0.65-1.5)
NNCD	9.5 (370)	¤	**1.1** (1.0-1.2)	-	-
Reference	8.9 (2948)		1.0		
LTMD (previous depression)					
No AED	10.0 (41)	0.96	**0.99** (0.72-1.4)	0.83	**0.95** (0.58-1.5)
AED	15.0 (36)	0.012	**1.6** (1.1-2.2)	0.094	**1.6** (0.92-2.7)
Epilepsy	11.9 (77)	0.14	**1.2** (0.94-1.5)	0.40	**1.2** (0.8-1.7)
NNCD	13.8 (1148)	¤	**1.5** (1.4-1.6)	-	-
Reference	10.1 (7561)		1.0		
SCL_D (current depression)					
No AED	3.7 (15)	0.12	**1.5** (0.90-2.5)	0.35	**1.4** (0.67-3.1)
AED	4.2 (10)	0.088	**1.7** (0.92-3.3)	0.20	**1.8** (0.73-2.9)
Epilepsy	3.9 (25)	0.023	**1.6** (1.1-2.4)	0.13	**1.6** (0.88-2.8)
NNCD	3.5 (292)	¤	**1.5** (1.3-1.7)	-	-
Reference	2.5 (1853)		1.0		
SCL_A (current anxiety)					
No AED	7.1 (29)	0.014	**1.6** (1.1-2.3)	0.057	**1.7** (0.99-3.0)
AED	6.7 (16)	0.11	**1.5** (0.91-2.5)	0.16	**1.7** (0.81-3.5)
Epilepsy	7.0 (45)	0.004	**1.6** (1.2-2.1)	0.018	**1.7** (1.1-2.6)
NNCD	6.2 (512)	¤	**1.4** (1.3-1.6)	-	-
Reference	4.6 (3422)		1.0		

¤ No significant difference between the NNCD versus 'Epilepsy all' groups. CI, confidence interval; SD, standard deviation; ASRS, Adult ADHD Self Report Scale; LTMD, Lifetime Major Depression Scale; SCL_D, Hopkins Symptom Check List for current depressive symptoms; SCL_A, Hopkins Symptom Check List for current anxiety symptoms.

S3 Table. Frequencies for self-reported diagnoses of ADHD, eating disorders, bipolar disorder and other (unspecified) psychiatric disorders in fathers with epilepsy with and without use of antiepileptic drugs (AEDs) compared to a reference group without epilepsy. Unadjusted and adjusted p-values and odds ratio (OR) are given for these comparisons. Fathers with non-neurological chronic disorders (NNCD) served as an additional internal control group.

	Frequencies	Unadjusted		Adjusted	
Group	**% (n)**	**p-Value**	**OR (CI)**	**p-Value**	**OR (CI)**
ADHD					
No AED	3.4 (6)	<0.001	**8.1** (3.5-18.6)	0.001	**5.1** (2.0-13.1)
AED	0.0 (0)	NA	NA	NA	NA
Epilepsy	2.2 (6)	0.002	**5.2** (2.3-11.8)	0.014	**3.2** (1.3-8.0)
NNCD	0.5 (18)	##	**1.1** (0.70-1.9)	-	-
Reference	0.4 (144)		1.0		
Eating disorders					
No AED	0.6 (1)	0.32	**2.6** (0.4-19.1)	0.35	**2.6** (0.35-18.6)
AED	0.0 (0)	NA	NA	NA	NA
Epilepsy	0.4 (1)	0.45	**1.7** (0.2-12.2)	0.63	**1.6** (0.23-11.8)
NNCD	0.3 (12)	¤	**1.6** (0.86-3.0)	-	-
Reference	0.2 (72)		1.0		
Bipolar disorder					
No AED	2.2 (4)	0.003	**7.0** (2.6-19.2)	0.008	**4.9** (1.5-15.7)
AED	1.0 (1)	0.28	**3.1** (0.4-22.5)	0.32	**2.8** (0.38-20.2)
Epilepsy	1.8 (5)	0.003	**5.6** (2.3-13.9)	0.007	**4.1** (1.5-11.2)
NNCD	0.5 (19)	#	**1.7** (1.0-2.7)	-	-
Reference	0.3 (110)		1.0		
Unspecified psychiatric disorders					
No AED	5.6 (10)	0.008	**2.6** (1.4-4.9)	0.004	**2.6** (1.4-4.9)
AED	2.0 (2)	1.00	**0.9** (0.2-3.6)	0.85	**0.88** (0.22-3.6)
Epilepsy	4.3 (12)	0.022	**2.0** (1.1-3.5)	0.025	**2.0** (1.1-3.5)
NNCD	3.5 (138)	¤	**1.8** (1.5-2.1)	-	-
Reference	2.3 (763)		1.0		

Significant difference between the NNCD versus 'Epilepsy all' groups: #p < 0.05; ##p < 0.01.

¤ No significant difference between the NNCD versus 'Epilepsy all' groups. CI, confidence interval; NA, not applicable.

S4 Table. Frequency of psychiatric symptoms (ADHD tested with ASRS, previous depression tested with LTMD, current depression tested with SCL_D and current anxiety tested with SCL_A), psychiatric diagnoses (ADHD, eating disorder, bipolar, unspecified psychiatric disorders), low satisfaction with life (SWLS) and low self-esteem (RSES) in fathers with epilepsy treated with antiepileptic drug (AED) polytherapy or monotherapy, compared to a reference group without epilepsy. Unadjusted p-values and odds ratios (OR) are given for these comparisons.

	Reference	**Polytherapy**			**Valproate monotherapy**			**Lamotrigine monotherapy**			**Carbamazepine monotherapy**		
	% (n)	% (n)	p	OR (CI)	% (n)	p	OR (CI)	% (n)	p	OR (CI)	% (n)	p	OR (CI)
Psychiatric symptoms													
ASRS (ADHD)	8.9 (2948	16.7 (2)	0.29	**2.1** (0.45-9.4)	9.5 (2)	0.71	**1.1** (0.25-4.6)	8.3 (2)	1.00	**0.93** (0.22-4.0)	11.1 (3)	0.73	**1.3** (0.39-4.3)
Previous depression	10.1 (7561)	20 (6)	0.12	**2.2** (0.91-4.5)	15.5 (9)	0.17	**1.6** (0.80-3.3)	17.9 (7)	0.11	**1.9** (0.86-4.4)	9.9 (9)	0.95	**0.98** (0.49-1.9)
Current depression	2.5 (1853)	3.4 (1)	0.52	**1.4** (0.19-10.3)	5.2 (3)	0.17	**2.1** (0.67-6.9)	5.1 (2)	0.25	**2.1**(0.51-8.8)	2.2 (2)	1.00	**1.0** (0.22-3.6)
Current anxiety	4.6 (3422)	3.4 (1)	1.00	**0.75** (0.10-5.5)	10.3 (6)	0.049	**2.4** (1.0-5.6)	7.7 (3)	0.43	**1.7** (0.54-5.7)	4.4 (4)	1.00	**0.97** (0.36-2.6)
Psychiatric diagnoses													
ADHD	0.4 (144)	0 (0.0)	NA	NA	0 (0.0)	NA	NA	0 (0.0)	NA	NA	0 (0.0)	NA	NA
Eating disorder	0.2 (72)	0 (0.0)	NA	NA	0 (0.0)	NA	NA	0 (0.0)	NA	NA	0 (0.0)	NA	NA
Bipolar	0.3 (110)	7.7 (1)	0.042	**25** (3.2-197.29)	0 (0.0)	NA	NA	0 (0.0)	NA	NA	0 (0.0)	NA	NA
Unspecified	2.3 (763)	0 (0.0)	NA	NA	0 (0.0)	NA	NA	4.2 (1)	0.42	**1.9** (0.25-13.9)	4.5 (1)	0.40	**2.1** (0.28-15.3)
Self-esteem and satisfaction with life													
Low self-esteem	1.3 (980)	3.3. (1)	0.33	**2.6** (0.35-19.0)	1.7 (1)	0.54	**1.3** (0.18-9.4)	5.1 (2)	0.93	**4.1** (0.98-16.9)	1.1 (1)	1.00	**0.83** (0.12-6.0)
Low satisfaction with life	0.7 (549)	3.4 (1)	0.19	**4.8** (0.66-35.6)	5.2 (3)	0.009	**7.4** (2.3-23.6)	0 (0.0)	NA	NA	1.1 (1)	0.49	**1.5** (0.21-10.8)

CI, confidence interval; SD, standard deviation; NA, not applicable; ASRS, Adult ADHD Self Report Scale; LTMD, Lifetime Major Depression Scale; SCL_D, Hopkins Symptom Check List for current depressive symptoms; SCL_A, Hopkins Symptom Check List for current anxiety symptoms; SWLS, Satisfaction With Life Scale" defined as score ≤ 9; RSES, Rosenberg Self-esteem scale.

Paper III

III

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Life satisfaction in women with epilepsy during and after pregnancy

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ABSTRACT

Objective: The aim of this study was to investigate life satisfaction in women with epilepsy during and after pregnancy.
Methods: The study was based on the Norwegian Mother and Child Cohort Study, including 112,288 women with and without epilepsy from the general population. Investigation took place at pregnancy weeks 15–19 and 6 and 18 months postpartum. Women with epilepsy were compared with a reference group without epilepsy.
Results: The proportion of women with epilepsy was 0.6–0.7% at all three time points. Women with epilepsy reported lower life satisfaction and self-esteem both during and after pregnancy compared with the references. Single parenting correlated negatively with life satisfaction in epilepsy during the whole study period. Epilepsy was associated with lower levels of relationship satisfaction and higher levels of work strain during pregnancy and lower levels of self-efficacy and satisfactory somatic health 18 months postpartum. Adverse life events, such as divorce, were more common in women with epilepsy compared with the references, and fewer women with epilepsy had a paid job 18 months postpartum.
Significance: Reduced life satisfaction associated with epilepsy during and after pregnancy showed that, even in a highly developed welfare society, women with epilepsy struggle. Mothers with epilepsy and their partners should be examined for emotional complaints and partnership satisfaction during and after pregnancy. Validated screening tools are available for such measures.

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1. Introduction

The prevalence of epilepsy varies between 0.7 and 1.3% in the general population [1], including women of fertile age. Emotional distress in pregnant women has negative effects on birth outcome [2], and birth anxiety and postpartum depression are more frequent in women with epilepsy [3]. They face the challenge of coping with antiepileptic drug (AED) treatment, balancing between risk of seizures and risk of teratogenicity [4]. Epilepsy can be stigmatizing, with a negative impact on emotional health and life satisfaction [5,6], adding to an already vulnerable situation during pregnancy. This has been demonstrated also for expecting fathers with epilepsy [7]. For most expecting parents, pregnancy is associated with positive anticipation and brings couples together with unique family ties. However, worries about the pregnancy, birth complications, and the baby's health may cause stress and anxiety. Transition into parenthood changes everyday life, and budgets become tighter. Some may feel loss of freedom due to the commitment and responsibility that comes with a new child. This can affect the couple's relationship [8] and add to the burden of specific epilepsy-related challenges during pregnancy. Relationship satisfaction and support from the partner is important for emotional health in both the mother and father [9] and even more so if challenged by a chronic disorder such as epilepsy.

Although the quantity of research on mental health in relation to pregnancy in women with epilepsy is increasing, studies focusing specifically on life satisfaction are missing. In this study, we examined different aspects of life satisfaction and life conditions in young women with epilepsy during and after pregnancy compared with women without epilepsy. Our hypothesis was that epilepsy is associated with more adverse aspects and challenges in the vulnerable time during and after pregnancy. We postulated that this is an epilepsy-specific effect and that extra challenges faced by women with epilepsy during gestation lead to a delay in convalescence after pregnancy.

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2. Material and method

2.1. Data collection

This longitudinal study included version 8 of the quality-assured data files from the prospective population-based Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health and described in detail elsewhere [10]. Data in the present study were from pregnancy weeks 15–19 and 6 and 18 months postpartum (Fig. 1). The women answered detailed questionnaires on past and current health issues, socioeconomic conditions, and lifestyle. Each pregnancy and the corresponding questionnaires were registered by a unique identification number. Through this identification number, data files from the compulsory Medical Birth Registry of Norway were connected to the MoBa files to attain supplementary data on health issues. Women pregnant again at 18 months postpartum were excluded at that time point from the present study (n = 10,648, Fig. 1). The study population constituted 102,265, 88,090, and 64,443 women at pregnancy weeks 15–19 and 6 and 18 months postpartum, respectively (Fig. 1). The group with epilepsy was compared with a reference group consisting of all mothers in MoBa without epilepsy at all three survey time points.

2.2. Variables

Different aspects for measuring life satisfaction are presented in Table 1 and included one specific item on global life satisfaction/quality of life, one item on relationship satisfaction, one item on self-esteem, one item on work strain, one item on quality of somatic health, and one item on general self-efficacy. All instruments and single questions used to assess the various aspects of life satisfaction in Table 1 are further elucidated and presented in Table S1. Global life satisfaction at pregnancy weeks 15–19 and six months postpartum was evaluated by the 5-item Satisfaction With Life Scale, a psychometric scale suitable for different age groups and cross-culturally [11]. Not all variables were consistently available at the three time points. This concerned, among others, the Satisfaction With Life Scale, which was not available 18 months postpartum. Since our study was conducted after the inclusion period in MoBa, we had no influence on the formulation of the questionnaires, and we do not know why the Norwegian Institute of Public Health chose not to include the same variables at each time point. Instead of the Satisfaction With Life Scale, we used an available screening question on quality of life from the World Health Organization's Quality of Life Instrument — Short Version to assess global life satisfaction 18 months postpartum. This instrument has been thoroughly evaluated and is used worldwide, and therefore is regard as suitable for epidemiological studies [12,13]. Both the Satisfaction With Life Scale and the World Health Organization's instrument are described in Table S1. From the World Health Organization's instrument, we also used a single question to assess Quality of Somatic Health 18 months postpartum. Self-esteem was evaluated through a 4-item short version of the original 10-item Rosenberg's Self-Esteem Scale [14], with a 0.95 correlation degree between the short and original scales [15]. The Relationship Satisfaction Scale, with 10 items constructed for MoBa, was used to assess partner support. The Relationship Satisfaction Scale is based on previously evaluated scales for marital and relationship satisfaction [16] and has showed good psychometric properties [17]. Work strain was constructed from 6 questions describing daily work situation (Table S1). This is not a formally validated instrument, and Cronbach's alpha (CA) was 0.59. The General Self-Efficacy Scale with 5 items was used to assess self-evaluation of coping with challenging and stressful situations. The scale is validated as a robust screening tool used cross-culturally [18] and has previously been used in the MoBa population [19]. At pregnancy weeks 15–19 and 6 and 18 months postpartum, CA was 0.75, 0.79, and 0.77 for the Rosenberg Self-Esteem Scale, and it was 0.91, 0.92, and 0.93 for the Relationship

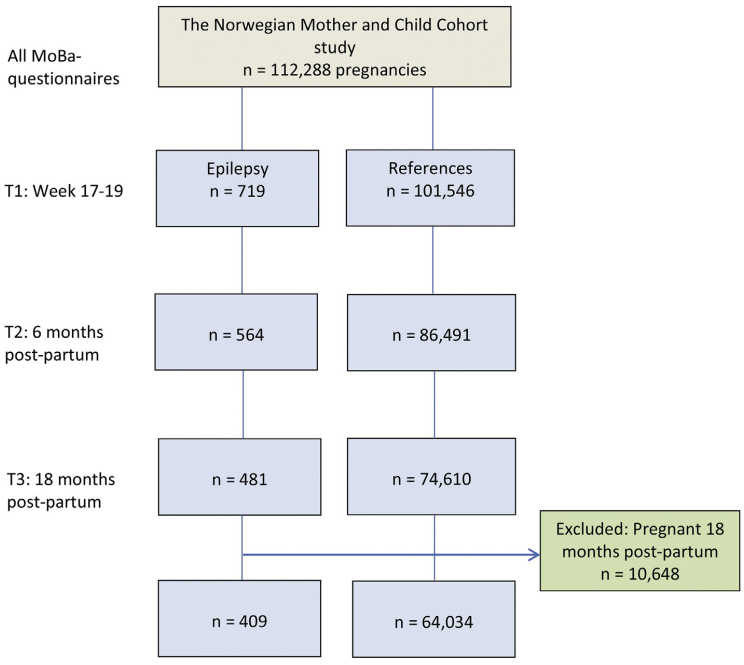

Fig. 1. Flow chart for study population based on the Norwegian Mother and Child Cohort Study (MoBa).

Table 1
Aspects of life satisfaction in women with and without epilepsy during pregnancy weeks 15–19 and 6 and 18 months postpartum.

Measures	Reference	Epilepsy	MD	CI	p
	Mean (SD)	Mean (SD)			
Pregnancy weeks 15–19					
Global life satisfaction	28.30 (5.34)	27.29 (5.99)	−1.02	−1.47 to −0.56	<0.001
Relationship satisfaction	53.06 (6.57)	52.46 (7.29)	−0.61	−1.16 to −0.05	0.034
Self-esteem	13.19 (1.98)	12.78 (2.15)	−0.42	−0.58 to −0.26	<0.001
Work strain	12.50 (2.72)	12.76 (2.85)	0.26	0.041–0.48	0.020
6 months postpartum					
Global life satisfaction	28.81 (4.91)	27.96 (5.55)	−0.85	−1.31 to −0.39	<0.001
Relationship satisfaction	52.61 (7.19)	52.23 (7.63)	−0.38	−0.99–0.23	0.22
Self-esteem	13.25 (2.03)	12.78 (2.20)	−0.47	−0.64 to −0.30	<0.001
18 months postpartum					
Global life satisfaction	4.41 (0.63)	4.27 (0.70)	−0.13	−0.20 to −0.07	<0.001
Relationship satisfaction	51.44 (7.97)	51.15 (8.21)	−0.29	−1.09–0.51	0.48
Self-esteem	13.10 (2.06)	12.71 (2.28)	−0.39	−0.61 to −0.17	0.001
Quality of somatic health	3.75 (0.2)	3.58 (1.04)	−0.17	−0.27 to −0.069	<0.001
General self-efficacy	15.49 (3.07)	14.91 (3.41)	−0.58	−0.91 to −0.24	0.001

Unadjusted linear regression. SD, standard deviation; MD, mean difference; CI, confidence interval. At pregnancy weeks 15–19 and 6 months postpartum, global life satisfaction was assessed through the Satisfaction With Life Scale, while at 18 months postpartum, a single question on quality of life was used. Values therefore differ noticeably between the first two and the last survey times.

Satisfaction Scale. At pregnancy weeks 15–19 and six months postpartum, CA was 0.89 for the Satisfaction With Life Scale, and 18 months postpartum, CA was 0.83 for the General Self-Efficacy Scale. Emotional distress (anxiety and depressive symptoms), assessed by the short version of the Hopkins symptoms check list [20], was included only as a predictor in regression analyses. Emotional distress in this group has been published previously [3,21].

In order to assess differences between the epilepsy and reference groups for distinct unfavorable scores on the various scales, additional dichotomous variables were computed for the screening instruments with a cutoff score. A score ≤nine on the Satisfaction With Life Scale indicates very low satisfaction [22]. Mean + 2SD was chosen as the cutoff for high scores on work strain. As the scores on the Relationship Satisfaction Scale were generally very high, we used mean − 1SD to define low relationship satisfaction. For the remaining scales, mean − 2SD was set as the cutoff for low scores. Social support was measured by three independent questions, using scales with grading between 1–3 and 1–5 (Table S1). 'No friends' was recorded when answering having no friends except her own partner. 'Reduced social contact' was defined as meeting or talking on the phone with people other than their partner less than once a month. A person was said to be 'feeling lonely' when answering 'usually' or 'almost always' to the question "Do you often feel lonely?". Data on specific adverse life events (yes/no) were available 6 and 18 months postpartum (Table S1).

Demographic variables included mother's age (years), low educational level (≤12 years), low income (≤26,704 Euro/year), lack of financial security (yes/no), sick leave independent of maternity leave (yes/no), unplanned pregnancy (yes/no), parity, and unemployment (yes/no). Low income was defined according to The European Commission as a household income per consumption unit <60% of the median [23,24]. Variables are described in the results or used in the analyses as classic confounders.

2.3. Statistics

International Business Machines SPSS Statistics 21.0 (SPSS Inc., Chicago, IL, USA) was used for analyses. For continuous outcomes, mean age and mean score of the screening instruments were compared through independent-samples t-test. Dichotomous variables were analyzed in cross-tabulation with Pearson's chi-square test and with Fisher's exact test when expected cell count was less than five. Results are presented as crude frequencies and unadjusted odds ratios (OR) with 95% confidence interval (CI) and corresponding p-values. Two-sided p-values <0.05 were considered statistically significant. The association between epilepsy and global life satisfaction was further analyzed by univariate and multivariate regression analyses. In some of these analyses, the independent, dichotomous variables were based on the screening tools with variable scales, as described above and in Table S1. In these analyses, the strength of correlation (B) was therefore not comparable between the various aspects but indicated the direction of the correlation. This is stated in the legends of the tables. To assess the associations between global life satisfaction and various life conditions for the group with epilepsy alone, separate univariate regression analyses were performed for this group. In order to assess the effect of epilepsy on global life satisfaction without over- or underadjustment for various covariates, we presented the results of stepwise analysis with groups of independent variables as shown in Table 2.

Table 2
Effect of epilepsy on global life satisfaction[a] with various adjustments during pregnancy weeks 15–19 and 6 and 18 months postpartum.

Measures	B	β	p
Pregnancy weeks 15–19			
Epilepsy I	−1.0 (−1.4 to −0.6)	−0.02	<0.001
Epilepsy II	−1.0 (−1.4 to −0.6)	−0.02	<0.001
Epilepsy III	−0.7 (−1.1 to −0.4)	−0.01	<0.001
Epilepsy IV	−0.7 (−1.1 to −0.4)	−0.01	<0.001
6 months postpartum			
Epilepsy I	−0.8 (−1.3 to −0.4)	−0.01	<0.001
Epilepsy II	−0.9 (−1.3 to −0.4)	−0.01	<0.001
Epilepsy III	−0.7 (−1.1 to −0.3)	−0.01	0.001
Epilepsy V	−0.5 (−0.9 to −0.1)	−0.008	0.013
18 months postpartum			
Epilepsy I	−0.1 (−0.2 to −0.07)	−0.02	<0.001
Epilepsy II	−0.1 (−0.2 to −0.07)	−0.02	<0.001
Epilepsy III	−0.1 (−0.2 to −0.05)	−0.01	<0.001
Epilepsy IV	−0.09 (−0.2 to −0.03)	−0.01	0.003
Epilepsy V	−0.08 (−0.1 to −0.02)	−0.01	0.012

B: Unstandardized regression coefficient in linear regression, indicating the direction of correlation between epilepsy and life satisfaction; CI, confidence interval. I: Epilepsy alone. II: Adjusted for epilepsy and age.
III: Adjusted for epilepsy, age, and socioeconomic aspects.
IV: Adjusted for epilepsy, age, socioeconomic aspects, and social support.
V: Adjusted for epilepsy, age, socioeconomic aspects, social support, and adverse life events.
[a] At pregnancy weeks 15–19 and 6 months postpartum, global life satisfaction was assessed through the Satisfaction With Life Scale, while at 18 months postpartum, a single question on quality of life from the WHO Quality of Life-BREF was used. B-values therefore differ noticeably between the first two and the last survey times.

Missing values in the screening instruments were treated with a maximum likelihood estimation procedure (imputation) to avoid potential sample distortions if ≤20% of the scale items were missing [25].

2.4. Ethics

The Norwegian Mother and Child Cohort Study has obtained a license from the Norwegian Data Inspectorate. The current study was approved by The Regional Committee for Medical Research Ethics (2010/788).

3. Results

3.1. Life satisfaction and social support

The proportion of women with epilepsy was similar at all three time points (0.6–0.7%) (Fig. 1). Women with epilepsy had lower mean scores for global life satisfaction and self-esteem at all three survey times compared with the references (Table 1). During pregnancy, the group with epilepsy had higher scores on work strain, and 18 months postpartum, they reported lower levels of general self-efficacy and quality of somatic health. The differences between the group with and without epilepsy were moderate but significant. Linear regression with adjustment for age, socioeconomic aspects, social support, and adverse life events showed that the association between epilepsy and global life satisfaction remained significant and with a negative correlation (Table 2).

For the distinct unfavorable scores, women with epilepsy more often reported low self-esteem than the references at all three time points (Fig. 2A–C). During pregnancy, low relationship satisfaction was more common in epilepsy and so were low global life satisfaction, low quality of somatic health, and low general self-efficacy 18 months postpartum. Complete unadjusted and adjusted numbers from Fig. 2A–C for the aspects with significant difference between the group with epilepsy and reference group are presented in Table S2. The table shows that, after regression analysis, the association between epilepsy and low self-esteem remained significant at all three time points and so did the correlation for low global life satisfaction, low quality of somatic health, and low general self-efficacy.

At all three survey times, single parenting showed the strongest negative correlation with life satisfaction (Table 3). Smoking, low income, low educational level, and sick leave also correlated negatively with life satisfaction during pregnancy and so did lack of financial security and adverse life events six months postpartum. At 18 months postpartum only, there was a significant and negative correlation between AED use and life satisfaction. Low self-esteem, low relationship satisfaction, emotional distress, low social support, high work strain, low general self-efficacy, and low quality of somatic health all correlated negatively with life satisfaction in women with epilepsy at all three time points (Table 4).

Women with epilepsy more often reported rare contacts with other persons than their partner during pregnancy and more often experienced feelings of loneliness 18 months postpartum, compared with the references (Fig. 2).

3.2. Socioeconomic aspects and adverse life events

Women with epilepsy were more often single compared with the references (Table 5). Pregnant women with epilepsy were more likely to have unplanned pregnancies and report sick leave. Lack of financial security was associated with epilepsy both 6 and 18 months postpartum. Not living with the child's father and unemployment were more common in women with epilepsy 18 months postpartum (Table 5).

Separation/divorce, worries about the child, conflicts with others, financial problems, and being seriously ill/injured were more common in women with epilepsy compared with the references both 6 and 18 months postpartum (Table 6). More women with epilepsy had experienced a serious accident/house fire/robbery six months postpartum than women without epilepsy, and reports on someone close being ill/injured were more frequent in women with epilepsy 18 months postpartum.

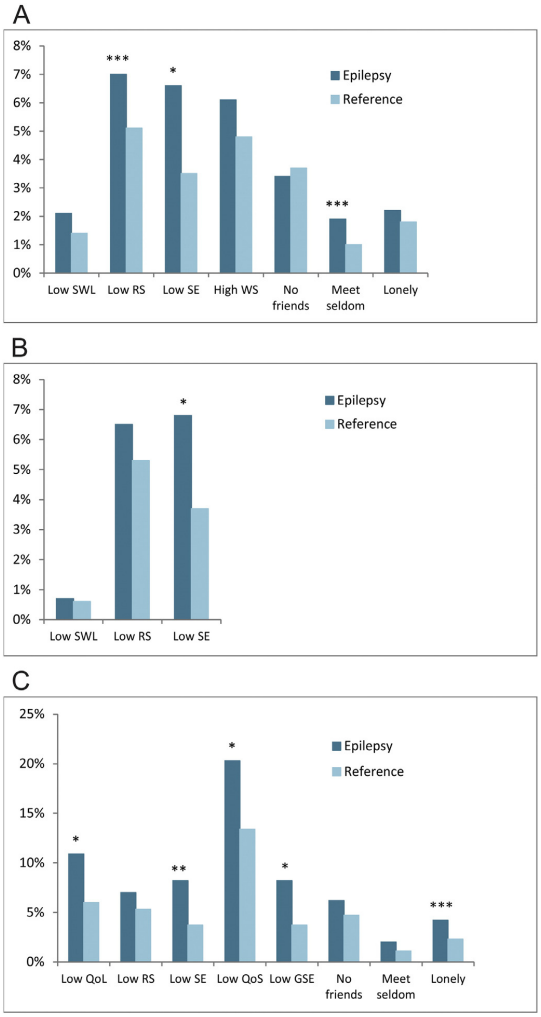

Fig. 2. Percentages of women reporting various aspects of low life satisfaction. Women with epilepsy are compared with the references without epilepsy. A) Pregnancy weeks 15–19, B) 6 months postpartum, C) 18 months postpartum. SWL, satisfaction with life; RS, relationship satisfaction; SE, self-esteem; WS, work strain; QoL, quality of life; QoS, quality of somatic health; GSE, general self-efficacy. 'No friends': No friends except partner. 'Meet seldom': Meeting or talking on the phone with people other than their partner <once a month. 'Lonely': Answering 'usually' or 'almost always' to the question "Do you often feel lonely?". Unadjusted numbers. Significance level (p): *<0.001, **<0.01, ***<0.05.

4. Discussion

4.1. Key findings

Life satisfaction was reduced in women with epilepsy during and after pregnancy, and they reported lower self-esteem and relationship

Table 3
Correlation between adverse socioeconomic aspects and global life satisfaction[a] in women with epilepsy during and after pregnancy.

Factors[b]	Pregnancy weeks 15–19			6 months postpartum			18 months postpartum		
	B (CI)	β	p	B (CI)	β	p	B (CI)	β	p
Single parenting	−6.2 (−8.4–4.0)	−0.2	<0.001	−7.0 (−9.2 to −4.7)	−0.3	<0.001	−0.5 (−0.7 to −0.2)	−0.2	0.001
Smoking during pregnancy	−3.9 (−5.4 to −2.4)	−0.2	<0.001	–	–	–	–	–	–
Low income	−3.1 (−4.2 to −1.9)	−0.2	<0.001	–	–	–	–	–	–
Low education	−2.5 (−3.4 to −1.5	−0.2	<0.001	–	–	–	–	–	–
Sick leave	−1.0 (−1.9 to −0.05)	−0.08	0.038	0.5 (−0.5–1.6)[c]	0.05	0.31	−0.1 (−0.2–0.2)	−0.009	0.86
AED use	0.3 (−0.6–1.3)	0.03	0.49	−0.9 (−1.9–0.04)	−0.08	0.059	−0.2 (−0.3 to −0.01)	−0.1	0.036
Age	0.009 (−0.08–0.1)	0.008	0.84	−0.04 (−0.1–0.06)	−0.03	0.45	−0.002 (−0.02–0.01)	−0.01	0.79
Lack of financial security	–	–	–	−3.8 (−5.2 to −2.4)	−0.3	<0.001	−0.4 (−0.6 to −0.2)	−0.2	0.001
Adverse life events	–	–	–	−2.4 (−3.3 to −1.5)	−0.2	<0.001	−0.3 (4.4–4.6)	−0.2	<0.001
Unemployment	–	–	–	–		–	−0.1 (−0.30–0.01)	−0.09	0.071

B: Unstandardized regression coefficient in univariate linear regression, indicating the direction of correlation between life satisfaction and adverse aspects; β, standardized regression coefficient; CI, confidence interval; AED, antiepileptic drug.

[a] At pregnancy weeks 15–19 and 6 months postpartum, global life satisfaction was assessed through the Satisfaction With Life Scale, while at 18 months postpartum, life satisfaction was assessed through a single question on quality of life from the WHO Quality of Life-BREF. B-values therefore differ noticeably between the first two and the last survey times.

[b] The adverse aspects are dichotomous variables, based on yes/no questions. The strength of correlation (B) is therefore comparable between the various aspects.

[c] Sick leave after pregnancy week 30 reported retrospectively at 6 months postpartum.

satisfaction. Epilepsy was associated with adverse socioeconomic aspects both during and after pregnancy, with single parenting showing the strongest negative correlation with life satisfaction in women with epilepsy. Low relationship satisfaction, low self-esteem, and emotional distress also correlated negatively with overall life satisfaction in women with epilepsy. The proportion of women with epilepsy reporting adverse life events was higher than in a reference group.

4.2. Strengths and limitations

To our knowledge, this is the first population-based study focusing specifically on life satisfaction in women with epilepsy during and after pregnancy. Life satisfaction and outcomes for women with epilepsy are important, especially in such a demanding period as during and after pregnancy. Recruitment from the general population has two major strengths. First, the population with epilepsy includes both AED-treated and untreated women, with no bias towards more severe epilepsy treated at specialized institutions. Second, as the reference group is heterogeneous and not only consists of healthy controls, the risk estimates reflect reliable differences without overestimation. Information on socioeconomic background data made it possible to adjust for confounders, and follow-up over time showed the true impact of the pregnancy. A validation study on the MoBa cohort concluded that prevalence estimates could be affected, with selection towards more favorable demographic aspects [26]. Despite such potential selection bias, associations between exposure such as epilepsy and AED use and outcome were unaffected. The prevalence of epilepsy in this and former studies based on this cohort is within the expected range [1]. A recent study found a near 100% diagnostic validity for the AED-treated women with epilepsy in our study population and with untreated women reporting inactive epilepsy [27]. Any potential selection bias would be expected to be similar in the group with epilepsy and reference group.

Loss to follow-up in longitudinal studies is a potential challenge. The participation rate of 40.6% of invited women at the beginning of the study is acceptable [26]. There is a risk that women who dropped out during the study were those with a greater burden of socioeconomic and health challenges. Also, some of the participants that became pregnant before 18 months postpartum might have had higher life satisfaction scores, leading to the decision of having another child. As the prevalence of epilepsy did not change during the follow-up period, potential selection bias and effects of dropping out should affect the group with epilepsy and reference group equally. The dropping out of 36% led to a population change so that comparisons of scores at different time points were not meaningful, but this did not affect the main aim of comparing epilepsy with nonepilepsy. A limitation is the lack of data on epileptic seizures and type of epilepsy. Seventeen percent reported seizures during pregnancy and 3% when giving birth, whereas 9% reported a worsening of epilepsy during pregnancy [27].

4.3. Interpretation

Our results show lower scores for life satisfaction during and after pregnancy in women with epilepsy. Depression is an important predictor of life satisfaction in epilepsy [28], and we have previously shown that depression is more common in our study population of women with epilepsy before, during, and after pregnancy, with a stronger association than for other nonepileptic chronic diseases [3,29]. Low

Table 4
Correlation between adverse aspects of life satisfaction and global life satisfaction[a] in women with epilepsy during and after pregnancy.

Factors[b]	Pregnancy weeks 15–19			6 months postpartum			18 months postpartum		
	B (CI)	β	p	B (CI)	β	p	B (CI)	β	p
Low self-esteem	−7.7 (−9.4 to −5.9)		<0.001	−8.9 (−10.6 to −7.2)	−0.4	<0.001	−1.0 (−1.2 to −0.7)	−0.3	<0.001
Low relationship satisfaction	−6.9 (−8.6 to −5.2)		<0.001	−9.8 (−11.5 to −8.2)	−0.5	<0.001	−0.7 (−1.0 to −0.4)	−0.3	<0.001
Emotional distress	−5.2 (−6.3 to −4.04)		<0.001	−6.5 (−7.8 to −5.3)	−0.4	<0.001	−0.7 (−0.9 to −0.6)	−0.4	<0.001
Low social support	−4.8 (−6.6 to −3.1)		<0.001	–	–	–	−0.3 (−0.9 to −0.6)	−0.1	0.006
High work strain	−4.01 (−5.9 to −2.1)		<0.001	–	–	–	–	–	–
General self-efficacy	–	–	–	–	–	–	−0.6 (−0.8 to −0.3)	−0.2	<0.001
Somatic health	–	–	–	–	–	–	−0.4 (−0.6 to −0.3)	−0.3	<0.001

B: Unstandardized regression coefficient in univariate linear regression, indicating the direction of correlation between life satisfaction and adverse aspects; β, standardized regression coefficient; CI, confidence interval; AED, antiepileptic drug.

[a] At pregnancy weeks 15–19 and 6 months postpartum, global life satisfaction was assessed through the Satisfaction With Life Scale, while at 18 months postpartum, life satisfaction was assessed through a single question on quality of life from the WHO Quality of Life-BREF. B-values therefore differ noticeably between the first two and the last survey times.

[b] The adverse aspects are dichotomous variables but based on scales with a different range. The strength of correlation (B) is therefore not comparable between the various aspects and only indicates the direction of the correlation.

Table 5
Characteristics of women with and without epilepsy during pregnancy weeks 15–19 and 6 and 18 months postpartum.

Measures	Reference	Epilepsy		
	% (n)	% (n)	OR (CI)	p
Pregnancy weeks 15–19				
Mean age (SD)	29.7 (4.7)	29.1 (4.9)	NA	<0.001
Education <12 years	35.8 (34,265)	51.8 (346)	1.9 (1.7–2.2)	<0.001
Low income	15.8 (15,365)	19.6 (131)	1.3 (1.1–1.6)	0.007
Unplanned pregnancy	19.5 (19,410)	23.9 (165)	1.3 (1.1–1.6)	0.003
Previously live born baby	48.1 (53,465)	46.7 (336)	0.94 (0.82–1.1)	0.48
In a relationship	96.6 (96,980)	94.1 (655)	0.56 (0.41–0.77)	<0.001
Sick leave >2 weeks	28.6 (27,627)	36.8 (243)	1.5 (1.2–1.7)	<0.001
6 months postpartum				
In a relationship	97.9 (83,161)	95.9 (536)	0.50 (0.33–0.77)	0.001
Sick leave after pregnancy week 30	64.5 (49,159)	67.5 (336)	1.1 (0.95–1.4)	0.17
Lack of financial security	16.6 (7110)	23.4 (63)	1.5 (1.2–2.0)	0.003
18 months postpartum				
In a relationship	95.9 (61,070)	92.6 (377)	0.54 (0.37–0.79)	0.001
Not living with the child's father	4.2 (2604)	7.2 (29)	1.8 (1.2–2.6)	0.002
Sick leave	21.8 (13,937)	23.5 (96)	1.1 (0.87–1.4)	0.42
Lack of financial security	6.8 (4336)	9.5 (39)	1.5 (1.0–2.0)	0.028
Unemployment	19.9 (12,491)	27.5 (110)	1.5 (1.2–1.9)	<0.001

Unadjusted p-values with odds ratio (OR) and confidence interval (CI).

score for global life satisfaction in the group with epilepsy during the whole study period, and after adjustment for socioeconomic factors, indicates that the low scores are likely to be linked to the epilepsy itself rather than confounding factors. Living with a chronic condition can be stigmatizing and influence emotional health and self-esteem negatively. Pregnancy is associated with positive expectations but at the same time implies a shift in life with new commitments and responsibility. For pregnant women with epilepsy, there are extra concerns about the mothers' and the fetuses' health due to seizures and teratogenicity from AED treatment [4]. Such worries may explain the reduced life satisfaction. We could not prove an association between life satisfaction and AED treatment during pregnancy and six months postpartum. This could indicate that side effects from the therapy are modest or that the epilepsy is well-controlled. The higher percentage of mothers with epilepsy than without epilepsy reporting low life satisfaction, low satisfaction with somatic health, unemployment, and lower self-efficacy 18 months postpartum may reflect a delay in convalescence. Unemployment with loss of network and lack of stimulation is associated with depression, which again reduces work capacity [30]. Adjusting for unemployment as a confounder did, however, not remove the association between low life satisfaction and epilepsy. Childbirth can have a positive impact on the mothers' emotional and somatic health, whereas the first year of parenthood may affect them negatively [9]. In Norway, maternity leave lasts 10–12 months. At 18 months, parents should have been back at work for some time. Family expansion implies more duties and less flexibility. Coping with a full-time job may stress mothers with a feeling of guilt of not sufficing as a full-time parent. Such factors may explain low life satisfaction reported by all mothers 18 months postpartum.

Table 6
Adverse life events during the past 12 months in women with and without epilepsy reported 6 and 18 months postpartum.

Life event	Reference	Epilepsy		
	% (n)	% (n)	OR (CI)	p
6 months postpartum				
Problems at work/study	8.6 (7344)	9.5 (52)	1.1 (0.84–1.5)	0.46
Financial problems	13.2 (11,169)	21.3 (115)	1.8 (1.5–2.2)	<0.001
Ended relationship/divorced	1.4 (1240)	2.9 (16)	2.9 (1.2–3.4)	0.005
Conflicts with others	16.1 (13,781)	20.7 (114)	1.4 (1.1–1.7)	0.004
Worries about child	16.1 (13,712)	24.3 (133)	1.7 (1.4–2.0)	<0.001
Seriously ill/injured	3.1 (2691)	5.6 (31)	1.8 (1.3–2.7)	0.001
Anyone close seriously ill/injured	13.3 (11,427)	14.3 (79)	1.1 (0.85–1.4)	0.51
Serious traffic accident/house fire/robbery	0.7 (588)	1.4 (8)	2.1 (1.1–4.3)	0.032
Lost someone close	9.3 (7995)	8.8 (49)	0.95 (0.71–1.3)	0.72
18 months postpartum				
Problems at work/study	21.5 (13,432)	22.9 (91)	1.1 (0.86–1.4)	0.51
Financial problems	19.4 (12,176)	24.6 (99)	1.4 (1.1–1.7)	0.009
Ended relationship/divorced	2.5 (1541)	4.5 (18)	1.9 (1.2–3.0)	0.009
Conflicts with others	19.7 (12,339)	25.8 (102)	1.4 (1.1–1.8)	0.003
Worries about child	9.1 (5717)	12.4 (50)	1.4 (1.0–1.9)	0.024
Seriously ill/injured	4.9 (3073)	9.2 (37)	2.0 (1.4–2.8)	<0.001
Anyone close seriously ill/injured	16.8 (10,515)	21.4 (86)	1.4 (1.1–1.7)	0.013
Serious traffic accident/house fire/robbery	1.1 (674)	1.2 (5)	1.2 (0.48–2.8)	0.63
Lost someone close	10.2 (6391)	13.4 (54)	1.4 (1.0–1.8)	0.031

Unadjusted p-values with odds ratio (OR) and confidence interval (CI).

Women with epilepsy reported an increased rate of separation from their partner postpartum compared with the references. We and others have previously shown that expecting women with epilepsy were also more likely to be single parents [5,21]. In addition to challenges met by all couples having children, the burden of living with a chronic condition implies particular strains on a couple's relationship [31]. Specific restrictions associated with epilepsy are absence from alcohol, regular daily routines with enough sleep, and sometimes car driving. These require extra support and flexibility from the partner when having a baby and could be a source of frustration between the partners. Concerns about side effects for the child from exposure to AEDs in breast milk is also a stress factor, although most AEDs are considered safe during breastfeeding [32]. Another specific challenge for mothers with epilepsy is situations when left alone with the child. Fear of harm to the child due to seizures causes anxiety and vulnerability [33]. This also affects the father, who needs to take a greater responsibility and be available for the mother and child. Epilepsy is associated with lower educational level and low income [5,21]. This total burden of epilepsy-specific concerns, emotional distress, low self-esteem, and adverse socioeconomic conditions may cause extra strain on the relationship and may partly account for the increased rate of partner separation in the mothers with epilepsy. In the peripartum period, many women feel vulnerable because they are more dependent on their partner and experience a decrease in self-esteem and emotional health due to changes in bodily appearance [9]. For women with epilepsy, perceived stigma due to their chronic condition is a predictor of low self-esteem and diminished life satisfaction [28].

Our findings demonstrate that low relationship satisfaction, low self-esteem, and emotional distress are important for life satisfaction in women with epilepsy during and after pregnancy. Having a partner is beneficial for social, economic, and psychological support [34], while lack of partner support is shown to be a risk factor for emotional dysfunction in both parents [9]. For persons with epilepsy, being married has a positive impact on specific epilepsy-related concerns, such as fear of being injured during a seizure [35], and irrespective of other social support, marriage has a positive effect on life satisfaction in persons with epilepsy [36].

5. Conclusions

Epilepsy is associated with lower life satisfaction during pregnancy and for 18 months postpartum. The participants experience adverse socioeconomic challenges important for life satisfaction, including partner separation and divorce. Relationship satisfaction shows an important association with life satisfaction during and after pregnancy. Given the elevated risks in women with epilepsy and the association between relationship satisfaction and general life satisfaction, we recommend that mothers with epilepsy and their partners should be given extra attention in the follow-up during and after pregnancy.

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Disclosures

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2016.06.025.

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Supplemental material paper III

Table S1. Variables in screening instruments and single questions used to assess different aspects of satisfaction with life.

Variables	Response options
Satisfaction With Life Scale	
Do you agree or disagree with the following statements?	
1. My life is largely what I wanted it to be	7 (1-7)[1]
2. My life is very good	7 (1-7)[1]
3. I am satisfied with my life	7 (1-7)[1]
4. To date, I have achieved what is important for me in my life	7 (1-7)[1]
If I could start all over, there is very little I would do differently	7 (1-7)[1]
Hopkins Symptom Checklist	
Have you been bothered by any of the following during the past two weeks?	
1. Feeling fearful	5 (1-5)[2]
2. Nervousness or shakiness inside	5 (1-5)[2]
3. Feeling hopeless about the future	5 (1-5)[2]
4. Feeling blue	5 (1-5)[2]
5. Worrying too much about things	5 (1-5)[2]
Relationship Satisfaction	
How well do these statements describe your relationship?	
1. I have a close relationship with my spouse/partner	6 (1-6)[3]
2. My partner and I have problems in our relationship	6 (1-6)[3]
3. I am very happy with our relationship	6 (1-6)[3]
4. My partner is generally understanding	6 (1-6)[3]
5. I often consider ending our relationship	6 (1-6)[3]
6. I am satisfied with my relationship with my partner	6 (1-6)[3]
7. We frequently disagree on important decisions	6 (1-6)[3]
8. I have been lucky in my choice of a partner	6 (1-6)[3]
9. We agree on how our child should be raised	6 (1-6)[3]
10. I believe my partner is satisfied with our relationship	6 (1-6)[3]
Rosenberg´s Self-Esteem Scale	
What kind of perception do you have of yourself?	
1. I have a positive attitude towards myself	4 (1-4)[4]
2. I feel really useless at times	4 (1-4)[4]
3. I feel that I don't have much to be proud of	4 (1-4)[4]
4. I feel that I'm a valuable person, on an equal footing with anyone else, at any rate	4 (1-4)[4]
World Health Organization's Quality of Life instrument-short version	
How would you rate your quality of life?	5 (1-5)[5]
How satisfied are you with your health?	5 (1-5)[6]

The General Self-Efficacy Scale	
How well do these statements describe you?	
1. I can always manage to solve difficult problems if I try hard enough	4 (1-4)[7]
2. If someone opposes me, I can find the means and ways to get what I want	4 (1-4)[7]
3. I am confident that I could deal efficiently with unexpected events	4 (1-4)[7]
4. I can remain calm when facing difficulties because I can rely on my coping abilities	4 (1-4)[7]
5. If I am in trouble, I can think of a good solution	4 (1-4)[7]
Work strains	
How do the following statements describe your work situation?	
1. My work is very stressful	4 (1-4)[8]
2. I learn a lot at work	4 (1-4)[8]
3. My work is very monotonous	4 (1-4)[8]
4. I am able to decide how my work is to be carried out	4 (1-4)[8]
5. There is a good team spirit at my place of work	4 (1-4)[8]
6. I enjoy my work	4 (1-4)[8]
Life events	
Have you experienced any of the following during the last 12 months?	
1. Problems at work	
2. Financial problems	No/ Yes
3. Divorce/separation	No/ Yes
4. Conflicts with family/friends/neighbours	No/ Yes
5. Concerns about the baby	No/ Yes
6. Serious personal injury/illness	No/ Yes
7. Close relative being injured/ill	No/ Yes
8. Involved in traffic accident/fire/robbery	No/ Yes
9. Lost someone close	No/ Yes
10. Exposed to physical violence.	No/ Yes
Social support	
Do you have anyone other than your husband/partner you can ask for advice in a difficult situation?	3 (1-3)[9]
How often do you meet or talk on the telephone with your family (other than your husband/partner and children) or close friends?	3 (1-3)[10]
Do you often feel lonely?	5 (1-5)[11]

1. Response option 1-7: “Disagree completely”, “Disagree”, “Disagree somewhat”, “Neither nor”, “Agree somewhat”, “Agree”, “Agree completely”.
2. Response option 1-5: “Never”, “Seldom”, “Sometimes”, “Often”, “Very often”.
3. “Agree completely”, “Agree”, “Agree somewhat”, “Disagree somewhat”, “Disagree”, “Disagree completely”
4. Response option 1-4: “Strongly agree”, “Agree”, “Disagree”, “Strongly disagree”.

5. “Very poor”, “Poor”, “Neither poor nor good”, “Good”, “Very good”
6. “Very dissatisfied”, “Dissatisfied”, “Neither satisfied nor dissatisfied”, “Satisfied”, “Very satisfied”
7. “Not at all true”, “Hardly true”, “Moderately true”, “Exactly true”
8. “Agree”, “Agree mostly”, “Disagree mostly”, “Disagree”
9. “No”, “Yes, 1 or 2 people”, “Yes, more than 2 people”
10. “Once a month or less”, “2-8 times a month”, “More than twice a week”
11. «Almost never”, “Infrequently”, “Sometimes”, “Usually”, “Almost always”

Table S2. Percentage and risk of low relationship satisfaction, low self-esteem, low quality of life, low quality of somatic health and low general self-efficacy in women with epilepsy compared to women without epilepsy.

			Unadjusted		Adjusted[#]	
	Reference	**Epilepsy**	**OR (CI)**	**p**	**OR (CI)**	**p**
Pregnancy week 15-19						
Low relationship satisfaction	5.1 (4923)	7.9 (46)	1.4 (1.0-1.9)	0.033	1.3 (1.0-1.8)	0.075
Low self-esteem	3.5 (3440)	6.6 (45)	2.0 (1.4-2.7)	<0.001	1.7 (1.3-2.3)	0.001
6 months postpartum						
Low self-esteem	3.7 (3186)	6.8 (38)	1.9 (1.4-2.7)	<0.001	1.7 (1.2-2.4)	0.002
18 months postpartum						
Low quality of life	6.0 (3791)	10.9 (44)	1.9 (1.4-2.6)	<0.001	1.7 (1.3-2.4)	<0.001
Low self-esteem	4.3 (2697)	7.5 (30)	1.8 (1.2-2.6)	0.002	1.6 (1.1-2.3)	0.014
Low quality of somatic health	13.4 (7089)	20.3 (66)	1.6 (1.3-2.2)	0.002	1.5 (1.2-2.0)	0.002
Low general self-efficacy	3.7 (2354)	8.2 (33)	2.3 (1.6-3.3)	<0.001	2.1 (1.5-3.1)	<0.001

OR, odds ratio; CI, confidence interval

#Adjustment for age, income, education, single parenting.