

Overweight and eating disorders in people with epilepsy

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Scientific environment

My work was carried out at the Department of Clinical Medicine, University of Bergen, and the Department of Neurology, Haukeland University Hospital. Our research group, Bergen Epilepsy Research Group (BERG) has been formally approved by the Department of Clinical Medicine. BERG is an active research group with more than 20 members, and is led by professor Nils Erik Gilhus, professor Bernt Engelsen and associate professor Marte Bjørk.

BERG has been focusing on mother and child related challenges in people with epilepsy, using data from the Norwegian Medical Birth Registry, the Norwegian Mother and Child Cohort Study and the Norwegian Prescription Registry. This has bridged into a pan-Nordic commitment in the SCAN-AED study (www.SCANAED.org), which are merging registries from Norway, Sweden, Denmark, Finland and Iceland.

Further, BERG is a multidisciplinary group, including neurologists, neurophysiologists, psychologist, obstetricians, pediatrician, pharmacologists, statisticians and epidemiologists. The group has several ongoing projects within epilepsy-related fields, including epidemiology, neurophysiology, and neuro-oncology. From Epilepsiforbundet there is a user representative.

BERG has received financial backing from Helse-Vest, University of Bergen, Torbjørg Hauges legat, Epilepsiforbundet and NordForsk.

Professor Morten Lossius and neurologist Kristin Alfstad of National Center for Epilepsy, Oslo, have been important partners for this particular work, as well as Norwegian Institute of Public Health, Oslo.

We cooperate with well renowned professionals and institutions, both nationally and internationally. Professor Torbjörn Tomson of Karolinska Institutet, Sweden, professor Mika Gissler and Maarit Leinonen of THL, Finland, senior researcher Jakob

Christensen and postdoc Julie Werenberg Dreier of Aarhus University Hospital and Aarhus University, Denmark, and professor Helga Zoega of the University of Iceland are main international research affiliates and collaborators.

Nationally, professor Olav Spigset of the Norwegian University of Science and Technology, Trondheim, senior researcher Kari Furu from Norwegian Institute of Public Health are partners of cooperation.



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Abstract

Background: Epilepsy is a common neurological disease and occurs in 0.7-1.3 % of the general population. It is associated with comorbid mental disorders such as depression and anxiety, and with a high risk for adverse outcome during pregnancy and delivery. Epilepsy affects people of all ages, but especially among young people it represents a challenge in how to cope with the disease. This makes young people with epilepsy a vulnerable group.

Aims: We hypothesized that young people with epilepsy have more eating disorders than the general population, and wanted to determine the prevalence of eating disorders among young people with epilepsy. A particular focus was put on pregnant women with epilepsy (WWE). We also wanted to investigate how comorbid eating disorders influence outcome of pregnancies in WWE. A second hypothesis we investigated was that young people with epilepsy are more overweight, and that such overweight leads to an increased risk for an adverse pregnancy-outcome in WWE.

Material and methods: We used the Norwegian Mother and Child Cohort Study (MoBa) to study pregnancies in WWE. More than 100.000 women were included in this cohort, whereas 706 women reported a diagnosis of epilepsy. We compared pregnancies in women with and without epilepsy in relation to eating disorders and overweight, and also pregnancy-outcome. MoBa is linked to the Norwegian Medical Birth Registry (MBRN). Secondly we used the Health Profile for Children and Youth in Akershus Study to study prevalence of eating disorders among youth with epilepsy of both genders. We investigated also additional variables such as overweight, diet and physical activity.

Results: We found that WWE have an increased rate of binge eating disorder compared to women without epilepsy. WWE were also more overweight and obese than the general population. Both of these variables were associated with adverse

outcome during pregnancy and delivery in WWE. Young people with epilepsy in Akershus were more likely to have had contact with health personnel due to eating disorders than the referent.

Conclusion: Pregnancies in WWE have a higher risk of adverse outcome. An increased rate of overweight and weight inducing eating disorders are contributing factors to this. The increased rate of eating disorders among people with epilepsy is evident from an early age, and this is important for health personnel to be aware of in their interaction with these patients. Early diagnosis and treatment is of great importance.

List of publications

- Kolstad E, Gilhus NE, Veiby G, Reiter SF, Lossius MI, Bjørk M (2015): "Epilepsy and eating disorders during pregnancy: Prevalence, complications and birth outcome", *Seizure*
- Kolstad E, Gilhus NE, Veiby G, Bjørk M (2016): "Overweight in epilepsy as a risk factor for pregnancy and delivery complications", *Epilepsia*
- Kolstad E, Bjørk M, Gilhus NE, Alfstad K, Clench-Aas J, Lossius M. (2017): "Young people with epilepsy have an increased risk of eating disorder and poor quality diet", *Epilepsia Open*

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Abbreviations

AED: Antiepileptic drugs

AN: Anorexia nervosa

Apgar score: A method to quickly summarize the health of newborn children

BED: Binge eating disorder

BMI: Body Mass Index

BN: Bulimia nervosa

ED: Eating disorder

EDNOS: Eating disorder not otherwise specified

EURAP: European and International Registry of Antiepileptic Drugs in Pregnancy

LGA: Large for gestational age

MBRN: Medical birth registry of Norway

MoBa: The Norwegian Mother and Child cohort study

NAAPR: North American AED Pregnancy Registry

SGA: Small for gestational age

SUDEP: Sudden unexpected death in epilepsy

WWE: Women with epilepsy

1. Epilepsy

1.1 Definition

The International League Against Epilepsy (ILAE) defined epilepsy in 2014 as (1):

A disease of the brain defined by any of the following conditions

1. At least two unprovoked (or reflex) seizures occurring >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

In this definition, there is a variety of different expressions of epileptic seizures. Classification and descriptions of seizures have therefore been of importance through history, and in 2017 ILAE proposed an updated version of “Operational classification of seizure types” (2). As seen in Figure 1 the classification separates focal, generalized and unknown onset as the main seizure characteristics. In focal onset seizure a description of awareness is considered next, and then motor- and nonmotor onset of seizure. Generalized onset epilepsy classifies further as motor or non-motor, with non-motor generalized epilepsy being absence seizures.

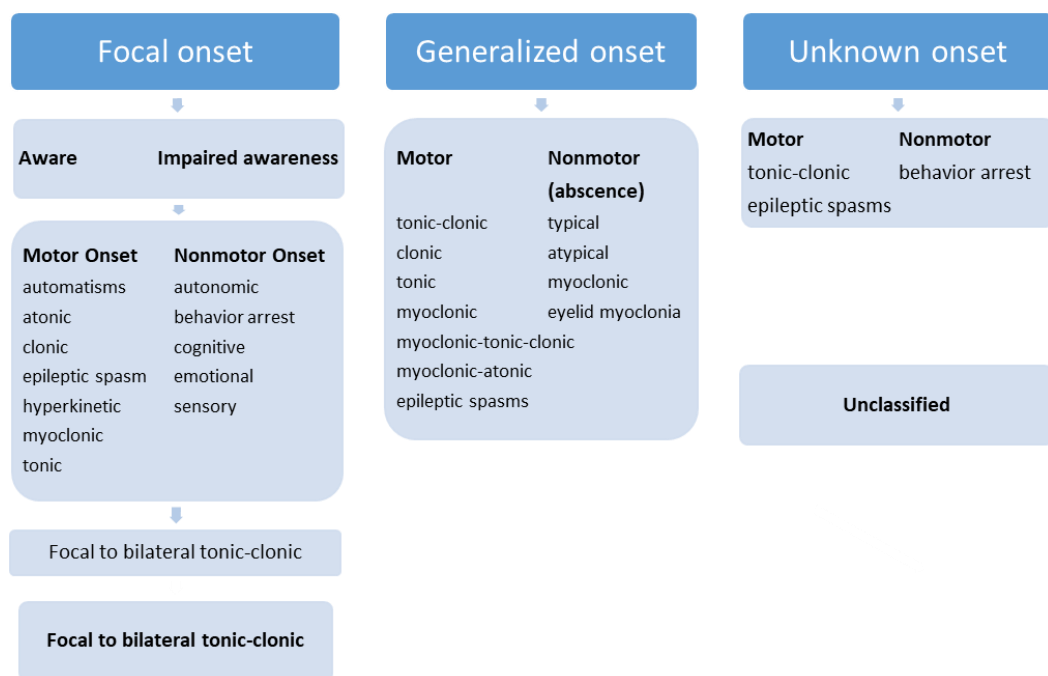


Figure 1: Based on “Operational classification of seizure types by the International League Against Epilepsy.” (2)

As well as a definition of epileptic seizures, there is of importance to classify epilepsy types. Throughout the 20th century the topic of epilepsy classification has sparked intense debate, and the ILAE have updated their terminology several times. In 1989 a revised version of classification of epilepsies and epileptic syndromes was authored (3) and this version has been highly influential worldwide and has had a major impact on epilepsy care and research (4). With time and further knowledge the ILAE felt the need to revise the classification of epilepsies and in 2017 *ILAE classification of the epilepsies position paper of the ILAE commission for classification and terminology* (4) was published.

In this new classification there are three levels (figure 2). The first level contains information about seizure type, which is thoroughly discussed in a separate paper (2), and this is discussed above and in figure 1.

The second level discusses epilepsy types, and contains four categories, 1) generalized, 2) focal, 3) combined general and focal, and 4) unknown. This level assumes that a patient has a diagnosis of epilepsy based on the current definition. A generalized epilepsy is made on clinical characteristics, but would typically be supported by an electroencephalography (EEG) of generalized spike-slow wave pattern (4). Focal epilepsy includes a range of seizure types, with and without impaired awareness, both motor and non-motor symptoms. This diagnosis is also based on clinical grounds, but supported by interictal epileptic activity in EEG. Patients with both focal and generalized seizures fit into the new group of combined generalized and focal epilepsies. The unknown category is used where a diagnosis of epilepsy has been concluded, but the physician is unable to determine whether it is a focal or generalized epilepsy due to insufficient information.

Epilepsy syndromes are labeled in level three. This refers to a cluster of symptoms containing seizure types, EEG and imaging features that occur together (4).

To determine the etiology of epileptic seizures is of great importance and this typically includes neuroimaging to determine structural pathology. There are five other etiological groups: Genetic, infectious, metabolic, immune and unknown.

The final perspective to be considered in epilepsy classification and terminology is comorbidity. Many epilepsies are associated with a range of comorbidities including intellectual disability, psychiatric challenges such as autism spectrum disorder, depression, and anxiety, as well as psychosocial concerns (4). Comorbidity will be covered extensively in this dissertation.

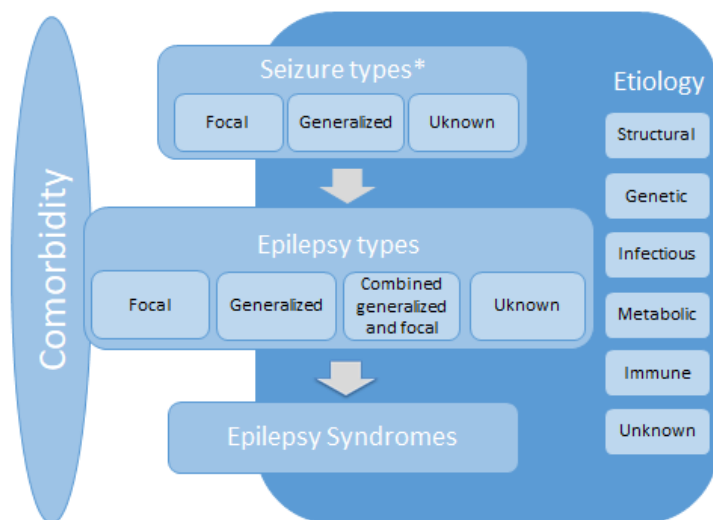


Figure 2: Framework for Classification of the Epilepsies, based on (4). *discussed in figure 1.

1.2 Epidemiology

Epilepsy is a common disorder in both children and adults. Population-based studies have shown incidence-rates in childhood to range from 0,5-8 per 1000 person-years (5-7), with a peak incidence within the first months of infancy. In adults the incidence rate of new-onset epilepsy varies with age, especially rising with every decade over 60 years (6). In a Norwegian review of prevalence and incidence in Nordic countries it was assumed that the incidence of new cases per 100.000 person-years was 30-60 (8), whereas the prevalence of active epilepsy was estimated to 0,6% (8). The prevalence of epilepsy varies in different parts of the world, with a marked difference between developed and non-developed countries. A review from China estimated a prevalence of 0,3% (9), and a study from Nigeria found a prevalence of 2,1% in rural communities and 0,5% in semirural communities (10).

In pregnant WWE, 0.5% used antiepileptic drugs 3 months before conception in Norway between 2005 and 2015 (11). This is in line with European prevalences. A

paper from 2015 reports that 0.51% of study-participants (n=1.248.713) were prescribed an AED during pregnancy, ranging from 0.43% to 0.60% depending of residing country (12)

1.3 Psychiatric comorbidity and stigma

Multiple epidemiological studies show an increased risk of psychiatric comorbidity in people with epilepsy, both in adulthood and in youth (13-18). Children with epilepsy have been found to have an increased risk of psychiatric comorbidity such as depression(19), anxiety(19), attention deficit(19) and hyperactivity disorder (ADHD) (19) and autism spectrum disorder (19) compared with children without epilepsy. This has been found in uncomplicated epilepsies, but is especially increased in complicated epilepsies. Complicated epilepsy is defined as: Epilepsy plus brain lesions resulting in impaired cognitive function (13, 20). Likewise is mental health issues more prevalent in adults with epilepsy, with increased risk of depression (16, 21, 22), anxiety (17, 18, 21), ADHD(21), cognitive impairment (23) and eating disorders (17, 24). In trying to understand the increased burden of psychiatric comorbidity in epilepsy, a theoretical framework of mediators have been proposed (20) (figure 3). Mediators include core epileptic characteristics such as early onset of seizures, duration of epilepsy, seizure drugs, and frequency and duration of seizures. Other potential mediators include epilepsy syndromes, underlying brain disorders and brain development and ageing, in addition to influences such as genotypic, psychological and sociocultural influences. This shows that increased psychiatric comorbidity in epilepsy is a multifaceted challenge, and few treatment options aside for seizure drug management and strategies adopted from the psychiatric profession are specific for people with epilepsy (20).

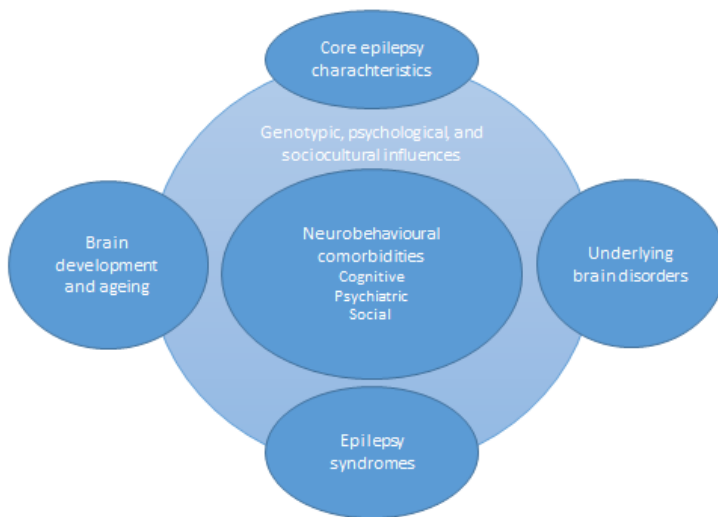


Figure 3, based on *Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan* (20)

1.3.1 Stigma

Historically, but also today, considerable stigma has been attached to people with epilepsy. Stigma is defined as a negative reaction by other to an attribute of a person that serves to spoil one's own social identity (25). Along with comorbidity and the seizures, stigma adds up to the total burden of epilepsy. Less social support, impaired social identity, humiliation and discrimination may be results of the stigma attached to epilepsy (25), which in turn leads to further social and economic morbidity and has the trademarks of a vicious cycle that is hard to interrupt. Few studies have studied the results of intervention with the purpose of reducing stigma, but it is widely agreed that public information and education is necessary (25). In 2008 a study from Germany compared public opinion of epilepsy through the 20th century and into the 21st century, using results from surveys who have been conducted five times since 1967 (26). Negative attitudes of epilepsy decreased in 2008 compared to 1967, with 18% in 2008 objecting to having a son or daughter marrying a person with epilepsy compared to 30% in 1967. In 2008, 11% did not think people with epilepsy should be

employed like other people, compared to 31% in 1967. In 1967 27% thought epilepsy was a form of insanity. This has decreased in 2008, but still 11% of persons asked thought epilepsy was a form of insanity. This perhaps illustrates stigma in epilepsy, which otherwise often can be hard to define or measure (26).

1.3.2 Treatment of psychiatric comorbidity

As psychiatric comorbidity are more frequent in people with epilepsy, focus must be on treating this in the same way as in the general population, if not better. Previously there has been a reluctance to prescribe antidepressants or anxiolytics to people with epilepsy, possibly due to fears over negative influence on seizure threshold. Hospital based studies from the 1980s and 1990s using high doses of tricyclic antidepressants raised questions of seizure induction (27-29). Follow-up studies in out-clinic patients did not support these concerns, but the idea persisted. This limited treatment within this group, and impairing quality- of-life (30). Later, antidepressants have been found to be anticonvulsive when investigated as a group (31). It is therefore of great importance that health personnel treating people with epilepsy is aware of this common misperception, and that people with epilepsy must be given the right medication when needed (32).

1.4 Pregnancy and offspring

1.4.1 Seizures in pregnancy

Most WVE have normal pregnancies and deliveries, but the threat of seizures during pregnancy and the effects seizures may cause on the foetus are of great concern to many. In terms of seizures it is the generalized tonic clonic seizures (GTCS) that are most feared. Seizure during labour is rare, but two case studies have shown bradycardia and asphyxiation in the foetus after a GTCS during labour (33). Seizures

during pregnancy have been associated with a significant higher preterm risk, a shorter gestational age, and a reduced birth weight (34, 35). In this study from Rauchenbach et al the 106 pregnant WWE also used antiepileptic drugs (AED) which are regarded as a confounding factor (34). Indications also point towards frequent seizures during pregnancy have a detrimental effect on neurodevelopment in the developing foetus (36). One study investigated 240 children born of mothers with epilepsy of 6 years or older. Of these, 80 children were born of mothers who did not use AEDs during pregnancy. Adab et al found that five or more GTCS during pregnancy was an independently risk factor for low IQ in the offspring (37). Studies with animal-models have found similar results. Novaes et al induced seizures in pregnant rats, and the offspring displayed impaired social behaviour (38), whereas Vale and coworkers found an effect on hippocampal interneurons in rat-pups with mothers who had seizures during pregnancy, as well as deficits in motor coordination and more immobility (39).

Status epilepticus is rare during pregnancy, in the large EURAP study there were 10 cases of convulsive status epilepticus of 3784 pregnancies reported (0,26%). Of these, there was one stillbirth and three children had major congenital malformations.

1.4.2 Maternal mortality

The increased risk of life-threatening pregnancy complications such as seizures, preeclampsia, and excessive bleeding postpartum, give rise to the thought of increased maternal mortality within the epilepsy population. In fact, two independent studies have shown a more than 10-fold increased mortality-rate for WWE compared to the general population (37, 40). Considering that the standard mortality rate is 2-3 times increased in people with epilepsy throughout life, shows that WWE is especially vulnerable during and after pregnancy (37). It is hypothesized that in addition to the aforementioned risk factors seizures, preeclampsia and postpartum bleeding, another explanation for the increased mortality rate could be sudden unexpected death in

epilepsy (SUDEP) (40). Sudden unexpected death is more than 20 times as common in people with epilepsy compared to the general population (41).

1.4.3 Complications during pregnancy

Regardless of seizure frequency, WWE have an increased risk of complications during pregnancy and delivery. Borthen and coworkers, using the MBRN, found that WWE had an increased risk of mild pre-eclampsia and preterm birth compared to women without epilepsy (42). Further, WWE and AED use had an increased risk of gestational hypertension and vaginal bleeding late in pregnancy (42). This was consolidated in a hospital-based study from the same research group where 205 consecutive deliveries at Haukeland University hospital with a confirmed diagnosis of epilepsy were retrospectively investigated and compared to 205 women without epilepsy with similar age and parity. WWE and AED use had an increased risk of severe preeclampsia and early vaginal bleeding (43). A systematic review published in the Lancet in 2015 where 38 papers and more than 2,8 million pregnancies were considered, there was an association between maternal epilepsy diagnosis and adverse maternal outcome such as spontaneous miscarriage, antepartum haemorrhage, postpartum haemorrhage, induction of labour, caesarean section, preterm birth and hypertensive disorders (44). Risk of adverse delivery outcome such as caesarean section, increased postpartum bleeding and low Apgar score was also found to be increased in WWE in Borthen and coworkers' investigation using the MBRN (45).

In relation to pregnancy and delivery, depression and anxiety are also complicating factors. Bjørk et al found in 2015 an increased risk of both in WWE using the Norwegian Mother and Child Cohort Study (MoBa) (46). They also found that the recovery rate was lower three years after delivery in WWE, and stresses the idea that it is important to identify patients at risk before delivery as symptoms of depression may be undertreated in this group.

Outcome of pregnancy in WWE does not only concern mothers, but the offspring as well. Questions have been raised in terms of how epilepsy influence development in the womb, but also long term effects such as cognitive effects in children born to mothers with epilepsy.

Veiby and coworkers found in 2013 that exposure to antiepileptic drugs during pregnancy was associated with impaired motor skills at the age of 6 months using the Norwegian Mother and Child cohort study (47). Use of multiple antiepileptic drugs was associated with worse outcome in children, both in terms of fine motor skills, but also in social skills, compared to infants with no such exposure. In this study, breastfeeding of the infant was not associated with harmful effects (47).

We have continued to study social skills and cognitive performance using the Norwegian Mother and Child cohort study, which in its prospective design enables researchers to follow children born of mothers with epilepsy. Veiby et al found an increased risk of autistic traits in children exposed to antiepileptic drugs in utero. The children were investigated at 18 months and 36 months of age (48). This has also consistently been found in other studies (49-51). What Bjørk et al were able to establish through a combination of self-reported information of use of folic acid preconceptionally and during pregnancy, and serumlevels of folic acid in gestational week 18-20, was that folic acid supplementation reduces the risk of autistic traits, especially in women using antiepileptic drugs (52). This shows that diet is of significance in pregnancy for WWE.

Studying verbal skills in children born to mothers with epilepsy in the Norwegian Mother and Child cohort study, Husebye et al found that AED-exposed children had a language delay compared to non-exposed children at 18 months and 36 months of age (53). Also in regards to development of language skills, folic acid supplementation used in the period from 4 weeks before conception through the first trimester, had a protective effect.

1.4.4 Pregnancy registries

Internationally there are three major population-based registries containing information about AED exposure, pregnancy- and infant outcome from the Northern hemisphere. These are the UK Epilepsy and Pregnancy register, the North American AED Pregnancy Registry, and European and International Registry of Antiepileptic Drugs in Pregnancy. They were all established in the late 1990s, where the UK register were the first to establish in 1997. The overall aims are similar for all three registries; to determine the risk of MCM in pregnancies exposed to prenatal use of AEDs (54), but there are some differences in methodology. These differences in methodology have made it difficult to merge or harmonize the different registries (54). The latest updates show that 5206 cases were included in the UK register (55), 9818 AED exposed women were included in NAAPR (56), and in EURAP 21.875 pregnancies were included in 2016 (57).

In Scandinavia, there is a good foundation for epidemiologic studies concerning pregnancy and birth, as all Scandinavian countries have national birth registries (58-60). This is a vast source of information, especially with its unique design of compulsory inclusion which will diminish selection bias in example.

All these registries have added invaluable knowledge about a wide range of issues concerning maternal health, and especially knowledge about outcome for pregnancies in WWE.

1.5 Treatment of epilepsy and anti-epileptic medication

1.5.1 Antiepileptic drugs

The overall idea in treating epilepsy is to prevent the occurrence of seizures. This is generally obtained in approximately 70% of cases when applying an antiepileptic drug

(61). Antiepileptic drugs are either classified by mechanism of action, or by efficacy spectrum. Because different drugs have different mechanisms of action and different efficacy spectrums, it is important to take into account seizure type, syndrome and other characteristics of the individual patient to be able to find the ideal antiepileptic drug.

Efficacy spectrum and choice of antiepileptic drug

The International League Against Epilepsy (ILAE) formed in 2006 guidelines for treatment with antiepileptic drugs by performing a structured literature review (62). These guidelines were updated in 2013 (63). Norwegian guidelines for treating epilepsy are based on these international reviews (64). When reviewing the literature the authors realized that many of the studies had major flaws, leading to poorly documented effects of antiepileptic drugs, especially in generalized seizures in adults, and in treatment of epilepsy in children (62). When choosing an antiepileptic drug in treatment of epilepsy it is important to weigh potential anti-epileptic effect vs potential adverse effect on an individualistic basis (62).

Treatment for focal onset seizures

There are four drugs with evidence level A, which means the effect of this drug is well established. Carbamazepine, levetiracetam, phenytoin and zonisamide have level A evidence of efficacy. Valproate has level B evidence, as effectiveness is regarded as probable in partial onset epilepsy. Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin have level C evidence, as they have a possible effect (63). When taking documentation for effectiveness into account, and weighing up possible adverse effects, Norwegian guidelines state oxcarbazepine, lamotrigine and levetiracetam as drugs of choice for focal onset epilepsy.

Treatment for generalized onset seizure

For this group there is less documented effect, due to lower quality of clinical trials. Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, topiramate and valproate have evidence level C. Gabapentin, levetiracetam and vigabatrin have level D, and are

regarded as having a potential effect (63). Norwegian guidelines states valproate as the drug of choice in general onset epilepsy, the one exception being fertile women. Second line of choice is levetiracetam, lamotrigine and topiramate (65).

Ethosuximide and valproate is effective against absence seizures (40, 63, 64).

1.5.2 Antiepileptic drug treatment during pregnancy

The association of major malformations in the offspring of mothers using antiepileptic drugs have had a growing awareness during the 20th century, which led to the EURAP epilepsy and other pregnancy registries. This is a cohort from 42 countries that prospectively monitor pregnancies exposed to monotherapy of antiepileptic drugs and in 2011 a paper comparing four different drugs (lamotrigine, carbamazepine, valproate, and phenobarbital) was published. Comparatively a low dose of lamotrigine had the lowest rates of major malformations in the offspring, whereas risks of malformations were significantly higher with valproic acid and phenobarbital, as well as higher doses of carbamazepine (66). A dose-dependency was seen for all four drugs. In 2016 a new paper was published from EURAP, now the cohort contained 7355 pregnancies exposed to antiepileptic drugs, and Tomson et al were able to compare eight different drugs (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate) (57). Again valproate and phenobarbital had the highest risk of malformations (10.3% and 6.5% of pregnancies respectively), and lamotrigine and levetiracetam were considered the safest options (2.9% and 2.8% respectively) (57).

Other pregnancy registries such as the North American AED Pregnancy Registry (NAAPR) and the UK Epilepsy and Pregnancy register have found similar results. Valproate and phenobarbital carries the significantly highest risk of major congenital malformations, whereas newer drugs such as lamotrigine and levetiracetam are safer options (55, 67, 68). It is stressed that even though lamotrigine has been found to be a

safe option in terms of MCM, seizure control is of great importance, and lamotrigine can in some cases be less effective compared to other antiepileptic drugs such as valproate (55).

A paper from the EURAP-study shows that seizure-control is reduced when valproate is withdrawn during pregnancy (69).

AED in monotherapy have been shown to have similar risk of intrauterine death and there has been shown no dose dependency, although Tomson et al found that polytherapy increased this risk; RR 1.4 (CI 1.1-1.7) compared to all monotherapies (70).

1.5.3 Unintended pregnancy

AEDs and hormonal contraceptions have a high risk of bidirectional interaction, and that decreases seizure control and failed contraceptive function may be a consequence (71). Failed contraceptive medication is an apparent reason for unplanned pregnancy, and one study found that one in four unplanned pregnancy in WWE was due to failed contraception. Also less than 55% of WWE had planned their pregnancy (72).

1.5.4 Catamenial epilepsy

Some women have increased seizure activity in relation to hormonal changes following the menstrual cycle. Typically clusters of seizures occur in the ovulatory and menses fase of the menstrual cycle. This is called catamenial epilepsy. It does not refer to a specific type of epilepsy, but to the rhythmicity in seizure occurrence. In addition to antiepileptic treatment as described in the previous chapter, treatment focuses on influencing hormonal changes with oral contraceptives (73).

Contraceptives with progesterone are most frequently used, but also acetazolamide can be used in some cases (73).

1.5.5 Other antiepileptic treatment

Surgical treatment

Surgery includes resection or destruction of parts of the brain with epileptic origin. Surgical treatment is an option to patients with drug-resistant focal epilepsy (40).

Neurostimulation

The most common mode of treatment with use of neurostimulation, is vagus nerve stimulation. Originally, vagus nerve stimulation was developed for patients with drug-resistant epilepsy who were not candidates for surgical treatment. Half of patients with vagus nerve stimulation reduces seizure frequency by 50% (74), although only 5% become seizure-free.

Ketogenic diet

Ketogenic diet is a well-established and well-documented mode of treatment of epilepsy in children (75), but there is less documentation in adults. In a small sized study from Norway four patients out of six with juvenile myoclonic epilepsy had >50% seizure reduction with the less restrictive modified Atkins diet (75). The modified Atkins diet restricts intake of carbohydrates to 15-20 g a day, and encourages food with a high fat content.

1.6 Epilepsy in youth

Epilepsy is the most common neurological disorder in youth with prevalence numbers varying between 0.05-1 % (76). Among offspring in the MoBa cohort the incidence rates during the first year 144 per 100.000 person-years, and 58 per 100.000 person-years when considering ages 1 to 10 years (5). In total 587 of 112.744 (0.5%) met the criteria for validated epilepsy-diagnosis.

1.6.1 Etiology

The underlying cause of epilepsy in youth are generally divided in to three categories, namely genetic, metabolic/structural and unknown (77).

Genetic causes

The idea of genetic epilepsy is that the disease is exclusively caused by mutations in the genome without environmental impact (77). Most types of genetic epilepsies begin in childhood and include childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, as well as more severe syndromes with often therapy resistant seizures such as Dravet syndrome and West syndrome.

Metabolic/structural causes

Almost any structural lesion or damage to the cerebral cortex can cause seizures and epilepsy. Metabolic disturbances such as high fever, hyponatremia, and hypocalcemia are perhaps the most common causes of seizures in youth. Ischemia perinatally, or later in life, head trauma, infections such as meningitis or encephalitis are all common disorders that can cause lesions with epileptic potential.

Unknown causes

In defining epilepsy etiology this category reflects the fact our knowledge in certain cases are limited, and we're not able to determine the exact cause (77).

1.6.2 Comorbidity

Psychiatric comorbidity is quite frequent in children and adolescents with epilepsy. Various studies have estimated that 21-60% of children with epilepsy have comorbid depression or anxiety (76). This is up to six times more than the general population, and also considerably higher than other children with chronic disease. Also children with complicated epilepsy have more comorbid psychopathology than children with uncomplicated epilepsy (76). There is thought to be multiple factors contributing to the development of comorbid psychopathology, and among others executive

dysfunction, male gender, and early onset epilepsy were seen as risk factors in a study from Norway (78). Sleep disorders have also elevates the risk in paediatric epilepsy compared to population-based data, and are especially elevated among those with comorbid psychopathology (79)

1.6.3 Cognition and education

A global cognitive impairment is more common in children and adolescents with epilepsy than in their peers in population based studies, and rates of intellectual disability range from 21-40% (80). This will lead to difficulties in school performance, and this is also reflected in the fact that more children with epilepsy receives special educational services (81, 82). Global cognitive difficulties are seen as the main contributor to a significant lower academic achievement among people with epilepsy. Adjusted for IQ, other factors such as early onset epilepsy, difficulties in school attendance and specific cognitive deficits are also seen as risk factors for lower academic achievement (80). In the literature there is a separation between low-achievement due to global cognitive impairment, and underachievement that is discrepant to IQ-levels. Youth with epilepsy are comparatively more prevalent in both categories (80). Early screening for educational difficulties is imperative for positive outcome, especially in cases where the academic underachievement is discrepant to IQ-levels (80).

1.6.4 Social aspects

Whatever reason for lower educational levels, inevitably this will have socioeconomic consequences. In the UK there is a strong correlation between epilepsy and living in socioeconomic deprived areas (83), and in Iceland low socioeconomic status was a risk factor for epilepsy (84). Low income and higher rates of unemployment are also features associated with persons with epilepsy (85). People with symptomatic epilepsy are less likely to have a partner and offspring than the referent (86, 87), and compared

to normal population there is a higher risk of being unfit to work (87). As well as lower socioeconomic status, persons with epilepsy are more likely to report reduced quality of life and emotional problems (85). Because of stigma, previously mentioned in chapter 1.3.1., there is a risk for social isolation and thus less possibilities of social interaction and building relationships (88).

1.7 Overweight

Worldwide overweight and obesity is a growing concern as prevalences continue to increase in adults (89), and overweight also increases in youth (90). In the US, more than 35% of adults were obese (BMI >30) in 2010, and almost 17% of youth (91).

Overweight and obesity represent huge and growing public health issue, with it being an essential risk factor for cardiovascular disease, type 2 diabetes and some cancers (92). Figure 4 illustrates how weightgain in kg increases the risk of disease, in example an increase of 5-8 kg increases the risk of type 2 diabetes with 100% (92) (figure 4).

Figure 4: Notable health risks of weight gain, Based on Ben Menachem (92)

Weight gain (kg)	Disease	Risk increase
1	Heart disease	3%
	Hypertension	5%
2-5	Hypertension	30%
5-8	Type 2 diabetes	100%
	Hypertension	75%
	Ischemic stroke	25%
11-20	Hypertension	300%
	Ischemic stroke	50%
>20	Hypertension	400%
	Ischemic stroke	100%

1.7.1 Epilepsy and overweight

Overweight and obesity is thought to be common in people with epilepsy, and in an adult US population they found that 55.2% of people with epilepsy was overweight, similar to the general US population (93).

Another study found that overweight people with epilepsy reported a poorer health compared to the general population in a study from Georgia and Tennessee. They also reported a lower family income and lower employment rates (94). People with epilepsy reported a higher rate of obesity and the authors highlights the need for further studies that examines the physiological and psychosocial interactions between epilepsy and overweight.

Overweight in general is a growing concern in the industrialized world, but also in some developing countries. In Norway, overweight has been scarcely studied in people with epilepsy.

1.7.2 Mechanisms for increased overweight in epilepsy

There are several possible mechanisms for increased overweight in epilepsy. Both structural, iatrogenic and social/environmental theories are suggested.

Silveira and coworkers showed that amygdaloid seizures activate hypothalamic nuclei that are prominently involved in reproductive function and reproductive endocrine secretion and this could explain clinical features such as PCOS and hypothalamic amenorrhea (95). Hypothalamic nuclei are also involved in feeding behavior (96). Feeding behavior could then be affected by seizures in the same way endocrine function is affected by hypothalamic neuroendocrine control of energy homeostasis (93).

One study in Canada studied children and adolescents with epilepsy in terms of physical activity and overweight. There were 79 young people with at least 3 months history of epilepsy compared to their siblings (n=99). Those with epilepsy were more likely to be overweight and were less active (97). A German study investigated social and physical activity in 136 people with epilepsy (98). They were significantly less active in regular sports activities than controls, and they also judged sports to be more dangerous than controls. Furthermore, in a clinical study, people with epilepsy had a significantly higher BMI than controls, as well as having less aerobic and muscle strength endurance (98). Other studies supports this (65, 98), and as people with epilepsy tend to be less physically active this leads to increased BMI, decreased aerobic endurance, poorer self-esteem, and higher levels of depression and anxiety (99).

Ben Menachem writes that the two most important factors for weight gain in people with epilepsy is social factors and use of antiepileptic drugs (AEDs) (92).

Furthermore there is known weight inducers such as valproate, carbamazepine and pregabalin, weight neutral AEDs include lamotrigine, gabapentin, pregabalin, vigabatrin and levetiracetam, whereas AEDs associated with weight loss include topiramate, zonisamide and felbamate (92).

1.7.3 Consequences

Obesity is a well-established risk factor for complications during pregnancy, such as preeclampsia and other hypertensive disorders(100-102), diabetes type 2(103, 104), miscarriage(105), caesarian delivery (106, 107) and induction of labour (108, 109).

The review of epilepsy in pregnancy published in Lancet had no mention of overweight or obesity in relation to pregnant WWE (44). This reflects that obesity is scarcely investigated in WWE, especially in relation to pregnancy and its outcome.

As overweight is a known risk factor for numerous adverse health effects in the general population there is a need to study this association further in people with

epilepsy. To what degree is overweight a health issue in people with epilepsy, and how does overweight influence comorbidity in people with epilepsy?

1.8 Eating disorders

Eating disorders have increased dramatically in frequency in the last 50-60 years, and did not pose a severe challenge until the late 1970s (110). Thus research on the subject was scarce, and before year 2000 there only existed papers from small clinical samples (111). The most common eating disorders are anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED), in which life-time prevalence in Norway is 8.7% , and which will be prevalent in 3.8% of the population at any time (111, 112). In the Norwegian Mother and Child cohort there is a prevalence of approximately 5% of eating disorders (113). Rai et al. described an increased rate of self-reported eating disorders in people with epilepsy compared to the general population (17), and Reiter et al. also found an increased rate of eating disorders in pregnant WWE compared to other pregnant women (24). However, the prevalence of eating disorders in people with epilepsy have been scarcely studied, and there is a need for further investigations.

1.8.1 Etiology

The etiology of eating disorders are largely unknown, but factors such as body dissatisfaction, depression or anxiety and low self-esteem seem to be precursors (110). Interpersonal experiences that have been most frequently associated as risk factors for eating disorders are abuse, trauma and teasing (110), although there is still some debate into what mechanisms play a part and to what degree these are prominent in developing and maintaining an eating disorder (110). A theory is that a central feature in anorexia nervosa is personality traits such as having an extreme need to control eating, but also to control other aspects in life (114). Other contributing

factors is sociocultural pressure to be thin, family influences, dieting, biological contributors and genetic predisposition(110). BED in pregnancy has also been found to be associated with lifetime sexual abuse, anxiety and depression (115).

1.8.2 Consequences

Eating disorders may influence birth and obstetric outcomes, similarly to epilepsy and overweight. A Finnish population-based register study compared women with eating disorders to referent women and found that women with AN and BN had significantly lower weight babies, whereas women with BED had higher weight babies (116). AN was also associated with premature birth and perinatal death, and women with BN had increased risk of babies with low Apgar score. Using the Norwegian Mother and Child cohort study, Bulik et al found that women with BED had higher weight babies, a higher risk of large for gestational age babies and caesarian section than the referent (117). The authors noted in this paper that the statistical power for the lower prevalent disorders such as AN and BN was inadequate to determine an association to adverse obstetric outcomes. As noted in chapter 1.8. the prevalence of eating disorders in people with epilepsy is largely unknown. The influence of eating disorders on outcome of pregnancy and delivery in WWE is also largely unknown and studies on this subject is needed.

1.8.3 Diagnostic criteria

The American Psychiatric Association's diagnostic manual of mental disorders, 4th edition (DSM-IV), was the most common diagnostic tool in which to classify mental disorders, and in example eating disorders. Figure 5 shows the diagnostic criteria of anorexia nervosa (AN), bulimia nervosa (BN), eating disorder not otherwise specified (EDNOS), and binge eating disorder (BED):

Anorexia nervosa (AN):

- Refusal to maintain body weight at or above a minimally normal weight for age and height (less than 85% of that expected).
- Intense fear of gaining weight or becoming fat, even though underweight
- Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on selfevaluation, or denial of the seriousness of the current low body weight.
- In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her period occur only following hormone, e.g. estrogen administration.)

Bulimia nervosa (BN):

- Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
 - 1) eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.
 - 2) a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)
- Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise.

Eating disorder not otherwise specified (EDNOS):

- For females, all of the criteria for AN are met except that the individual has regular menses
- All of the criteria for AN are met except that, despite significant weight loss, the individual's current weight is in the normal range.
- All of the criteria for BN are met, except that the binge eating and inappropriate compensatory mechanisms occur at a frequency of less than twice a week or for a duration of less than 3 months
- The regular use of inappropriate compensatory behavior by an individual of normal body weight after small amounts of food (e.g., self-induced vomiting after the consumption of two cookies).
- Repeatedly chewing and spitting out, but not swallowing, large amounts of food.

Binge eating disorder (BED):

- Recurrent episodes of binge eating in the absence of the regular use of inappropriate compensatory behaviors of BN

Figure 5: Diagnostic criteria for eating disorders in DSM-IV.

2. Aims

Our main aim in this thesis was to determine how overweight and eating behavior are distributed in people with epilepsy, and whether findings were consistent when examining different study-populations. We also wanted to investigate predictors and consequences of overweight and eating disorders.

Paper 1: To determine the prevalence of eating disorders in pregnant WWE. Further, we wanted to examine how eating disorders influence pregnancies in WWE.

Paper 2: To determine whether WWE are more overweight than other women, and to investigate the effects of, and interactions between, overweight and epilepsy combined on pregnancy and obstetric outcome.

Paper 3: Finally, we aimed to study whether youth with epilepsy are more overweight, have an increased risk of eating disorders, and to determine quality of diet compared to youth without epilepsy.

3. Method

3.1 The Norwegian Mother and Child Cohort Study.

3.1.1 Data material

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based study, which recruited pregnant women in Norway from 1999 to 2008. The objective of Moba was to test specific aetiological hypotheses by estimating the association between exposures and diseases, aiming at prevention (118). It included more than 100.000 women and information about their pregnancies, general health and social situation was gathered through comprehensive questionnaires. Pregnant women from all over Norway were invited to participate prior to a scheduled ultrasound examination in gestational week 18-20. The first questionnaires were sent to participants in week 13-17 (Q1). Follow-up questionnaires were sent in gestational week 22 (Q2) and 30 (Q3). Thereafter questionnaires were sent 6 months (Q4), 18 months (Q5), 36 months (Q6), 5 years (Q-5year), 6 years (Q-6year), 7 years (Q-7year) and 8 years (Q-8year) after delivery. It is planned to follow the cohort further, and questionnaires are still being gathered. The recruitment included 50 of Norway's 52 hospitals with maternity units, and the overall response rate was 41% (119). In paper 1 and 2 questions from Q1 and Q4 were used. In our version of the MoBa cohort there were totally 106.508 pregnancies, whereas 706 reported having epilepsy for paper 1. For paper 2, the cohort was updated and now contained in total 107.516 pregnancies, with 713 cases of pregnancies with reported maternal epilepsy.

3.1.2 Medical Birth Registry of Norway

MBRN is a compulsory registry for all pregnancies and deliveries in Norway. The registry was established in 1967 and is run by the Norwegian Institute of Public Health (120). Midwives and general practitioners register information about maternal health during pregnancy, as well as birth outcome. The register is linked to the National Population Register to ensure a complete registration of all births in Norway. MBRN is linked to MoBa through an anonymous code, and we were therefore able to gain supplementary information about maternal health and birth outcome.

3.1.3 Variables and outcomes

The diagnosis of epilepsy was self-reported in MoBa, where participants answered yes or no to a question of whether they have or have had epilepsy. AED use was defined through three pathways:

- 1) Reported AED use in MoBa through a predefined yes/no question in MoBa
- 2) Or having reported an epilepsy diagnosis in MoBa and provided information about AED use in free-text answer
- 3) Or reported diagnosis of epilepsy in both MoBa and MBRN, and a registered use of AED in MBRN.

MoBa questionnaires were made in accordance with DSM-IV criteria for eating disorders. When trying to comply with the diagnostic criteria of eating disorders in paper 1, there were some adjustments that were needed. For AN the fourth criteria concerning amenorrhea had to be removed due to the fact MoBa consists of pregnant women. This criterion has also been removed in the new version of the manual – DSM-V. In the EDNOS category we focused on criterion 2, which was called impaired bodyimage and AN criteria are met except low BMI and amenorrhea, and criterion 6; BED.

In paper 1 we investigated associations between maternal epilepsy and ED, and how this influenced pregnancies in terms of hypertension, diabetes, preeclampsia, caesarian section, peripartum depression and/or anxiety (22), weight gain during pregnancy, SGA (121), LGA (121) and ponderal index. In paper 2 associations between maternal epilepsy and overweight, and how this influenced outcome in pregnancy for the same variables as in paper 1.

Overweight was defined as body mass index ($BMI = \text{weight}/\text{height}^2$) > 25 , and obesity as $BMI > 30$.

3.2 Health Profile for Children and Youth in Akershus Study

3.2.1 Data material

Health Profile for Children and Youth in Akershus Study is a cross-sectional population based study (122). The study was conducted by the Norwegian Health Services Research Centre in 2002. School classes from all municipalities in Akershus County were randomly selected, and all pupils aged 13-19 years in the chosen classes were invited to participate. Parents were informed and had to give their written consent. Questionnaires containing 110 questions regarding main topics such as: sociodemographic conditions, social network and school, smoking, alcohol, drug abuse, nutrition and attitude concerning body, physical health, psychosocial health, mental health, use of health services(14). The questionnaires were completed during a classroom session and were all anonymous. As many as 19.995 adolescents answered, yielding an 85 % response rate.

3.2.2 Variables and outcomes

The participants had the opportunity to report a diagnosis of epilepsy and this defined the epilepsy group. This question could be answered by “yes”, “no” or “don’t know”. The answer “yes” counted as having epilepsy and “no” and “don’t know” counted as not having epilepsy. A total of 247 individuals (1.2%) reported a diagnosis of epilepsy. All other participants constructed the reference group (n=19.748). Individuals reporting a diagnosis of asthma formed a control group of chronic disease (n=3.320), participants with asthma were also included in the reference group. Participants reported if they had been in contact with school nurse or other health personnel regarding eating disorders and this defined eating disorders in this cohort. Before conducting the study, an unhealthy diet was defined by a group of nutritionists as eating or drinking candy, potato chips, French fries, or sugar containing soda daily. We constructed a dichotomous variable of physical activity where the cut-off was set at being physically active two or more times a week. Participants reported if they were currently on a diet or had been in the past. Mean age of menarche was calculated for female participants. We calculated BMI with the help of an age adjusted scale from the World Health Organization (123).

3.3 Statistics

3.3.1 Statistical methods

When computing data we used IBM SPSS Statistics version 21. We studied differences between groups using Student’s t-test and Pearson’s chi-square test. Comparable groups were tested for variance using either Q-plotting or Levenes test. With an expected count of any cross-table was under 5, we used Fisher’s exact test. P-values of < 0.05 were considered statistically significant. To estimate the odds ratios (OR) with 95% confidence interval (CI) we used binary logistic regression. Using this method we were able to adjust for possible confounders such as maternal age, parity,

smoking, and socioeconomic factors (low household income, low education, and/or being a single mother) in paper 1 and 2. In paper 3 we were able to adjust for reported low family income and living with a single parent.

3.3.2 Additive and synergistic effects

By introducing an interaction term to the regression model in paper 2 we investigated whether there was a potentiating effect of epilepsy and overweight on complications during pregnancy or delivery. Potentiating effect was defined as an increased effect compared to the expected cumulative risk of two factors, whereas additive effect was defined as epilepsy and overweight having an independent and cumulative effect on risk estimates. We compared groups of 1) WWE + overweight to normalweight WWE and 2) WWE + overweight to overweight women without epilepsy. When both comparisons were statistically significant we regarded the effect as an additive risk. To determine potentiating risk, an interaction term was inserted as a variable, multiplying epilepsy x overweight. If the interaction variable was significant in the regression model, we regarded the effect as potentiating.

3.4 Ethics

The MoBa study was approved by the Regional Ethics Committee (REK nr 2011/1616), this was also the case for Health Profile for Children and Youth in Akershus study (REK ref. 40-02022). Participants were included by informed consent, inclusion was voluntary and data was anonymous to researchers. Participants had the option of study-withdrawal at any time. In publishing information of adverse risk factors, there is a potential for stigmatization of WWE. These factors were considered when discussing cost vs benefit, and we conclude that the benefits of further knowledge in this field outweigh the possible negative implications. Further

awareness of risk factors concerning overweight and eating disorders in people with epilepsy enables health personnel to take proactive measures.

4. Results

4.1 Paper I

In our first paper, *Epilepsy and eating disorders during pregnancy: Prevalence, complications and birth outcome*, we found that WWE had a significantly increased rate of BED during pregnancy (6.5% vs. 4.7%, $p<0.05$) and impaired bodyimage (6.1% vs. 3.6%, $p<0.05$) compared to the referent. We found no differences between groups in terms of rates of anorexia nervosa or bulimia nervosa. WWE and comorbid eating disorder had an increased risk of peripartum depression and/or anxiety than the referent (OR 2.17, CI 1.4-3.4) and operative delivery (OR 1.96, CI 1.3-3.0) after adjusting for confounding factors. WWE and comorbid eating disorder also had significantly more preeclampsia (7.9% vs 3.7%, $p<0.05$) than women without epilepsy. When adjusting for confounding factors this was no longer significant. We found that WWE had a significantly higher mean BMI than other women (24.7 vs. 24.0, $p<0.001$).

4.2 Paper II

Our second paper, *Overweight in epilepsy as a risk factor for pregnancy and delivery complications*, showed that WWE had higher weight (69.5 kg vs 68.0 kg, $p<0.01$) and BMI (24.7 vs. 24.0, $p<0.001$) prepregnancy than other women. WWE were also significantly younger (29.2 years vs. 29.8 years, $p<0.01$) than non-epilepsy women, and had more adverse socioeconomic factors (single mother, low educational level and low household income) (16.4% vs 9.5 %, $p<0.001$). WWE were more overweight (38.4% vs 31.3%, $p<0.001$) and obese (13.2% vs 9.6%, $p<0.01$) than women without epilepsy. Women using carbamazepine had the highest rate of overweight with 49.4%

being overweight, and women using valproate had the highest rate of obesity (20.8%). Women using lamotrigine were not significantly different to women without epilepsy in terms of overweight or obesity.

- Compared to normal-weight women without epilepsy, WWE and overweight had a significantly increased risk of all adverse pregnancy and delivery outcomes tested, except for SGA weight and SGA head circumference.
- When adjusted for covariates of adverse socioeconomic factors, WWE and overweight had a significantly increased risk of caesarean section, excessive bleeding during delivery and severe depression and anxiety symptoms compared to overweight women without epilepsy.
- Compared to normalweight WWE, overweight WWE had an increased risk of caesarean section, preeclampsia, gestational hypertension and neonatal transfer of the child to a pediatric unit.
- Overweight women using lamotrigine (n=38) had a significantly higher risk of caesarean section, severe depression and anxiety peripartum, SGA infants (2.5th percentile) and neonatal transfer than overweight women without epilepsy.
- Overweight women using valproate (n=22) had no significant increased risk of any adverse outcomes tested compared to overweight women without epilepsy, whereas overweight women using carbamazepine (n=41) had an increased risk of SGA (10th percentile) compared to overweight women without epilepsy.

4.3 Paper III

In our third paper, *Young people with epilepsy have an increased risk of eating disorder and poor quality diet*, we studied individuals between 13 and 19 years of age. We found an increased risk of reported eating disorder in the epilepsy group

compared to the referent (aOR 1.79, CI 1.0-3.0). There was also an increased risk of having an unhealthy diet (aOR 1.67, CI 1.3-2.2) and youth with epilepsy were less satisfied with their own appearance (aOR 0.69, CI 0.5-0.9). There were no differences in mean weight or BMI between groups. Individuals in the epilepsy group were more likely to smoke than the reference group (32.9% vs 24.2%, $p < 0.01$).

There were some gender differences in our study. Females with epilepsy were more likely to have a daily consumption of sugar-containing soda, potato chips, candy, or French fries than females without epilepsy (aOR 2.16, CI 1.5-3.2). Males with epilepsy were more often dieting than males in the reference group (aOR 3.12, CI 1.2-7.9), and also reported being less satisfied with their looks (aOR 0.44, CI 0.3-0.7). Dieting and poor satisfaction with own appearance did not feature as prominently in females with epilepsy. In a multivariate model we found an association between having an eating disorder and dieting within the epilepsy group (OR 47.9, CI 4.5-512), as well as an inverse association between satisfaction with own appearance and dieting (OR 0.05, CI 0.01-0.2).

A group consisting of youth with asthma scored between the epilepsy group and the referent for all variables tested.

5. Discussion

5.1 Methodological considerations

5.1.1 Population-based studies

This study includes observations from two population-based materials. MoBa is a prospective cohort study which is linked to MBRN, and the Health Profile for Children and Youth in Akershus is a cross-sectional study. Population-based questionnaire studies have many strengths and some limitations. Population based cohorts or cross sectional studies typically have large numbers of participants that increase statistical power. Population-based studies also provide study subjects with a wider range of disease severity compared to hospital-based populations. The main limitation is the lack of detailed clinical information, for example a precise diagnosis of epilepsy and epilepsy severity. With this methodology there is no randomization of exposure, and this makes observational studies more vulnerable to systematic errors.

5.1.2 Bias

Any comparison of groups in research with the ambition of detecting significant differences between these groups, aims at detecting the true difference. Selection bias is one important aspect that can skew results away from detection of true differences. Recall bias is another such factor.

Selection bias

Selection bias includes all are factors that influence or distort study participation. This results in a skewed relation of exposure and outcome in those who participate, compared to all those who theoretically should have been eligible for the study (124). In our case with MoBa, an example would be that people with epilepsy as a group often have lower educational levels, more cognitive challenges, and more mental

health issues than other women. This means that regarding inclusion into a study of this scale, with multiple and time consuming questionnaires to complete, a higher proportion of educated and intellectually well-functioning women might be included, and the inclusion rate of only 41% (119) may reflect this point. Women with severe epilepsy, which often includes cognitive impairment, are probably rarely included in MoBa. This will skew results in a way that had all WWE been included, also all women scoring in the lower brackets on scales for cognitive performance, education and mental health, the differences compared to other women in outcome such as eating disorders and overweight would be expected to be even greater. On the other hand a study considering selection bias in MoBa found that the prevalence of epilepsy \approx 0,7% is similar to that of the general population in Norway (125). This may reflect that inclusion of women with cognitive challenges and/or mental health issues in the non-epilepsy group is also rare.

With an inclusion rate of only 41% there is a wide range of possible selection biases, and motivation for study-inclusion may differ among groups. In chapter 1.3.1 stigma in epilepsy is considered. WWE will be aware of the stigma attached to a diagnosis of epilepsy, and perhaps especially in relation to pregnancy. This can influence their willingness to participate, thinking they don't want to highlight possible flaws and preexisting notions about risk assessment in pregnancy in WWE. This may be particularly evident in high risk pregnancies, such as women who have frequent seizures or use high dosages of AEDs.

MoBa is a register where only pregnant women are included. Women who are able to get pregnant are generally part of the more healthy part of the population. For anorexia nervosa, one diagnostic criteria is amenorrhea. Individuals with anorexia nervosa has therefore a decreased chance of becoming pregnant. This creates a selection bias as very few with symptomatic anorexia nervosa will be included in MoBa. To avoid this bias the criterion of amenorrhea for anorexia nervosa was excluded in our study.

Another selection bias in MoBa was due to the questionnaires only being available in Norwegian, excluding some women with background from ethnic minorities.

In the Health Profile for Children and Youth in Akershus study the study design was different in that chosen participants had to fill out questionnaires during school hours. This made the participation rate much higher, 85% (126), which probably will make selection bias/volunteer bias less pronounced. All children in the chosen schools were invited to participate. Also because of the high response rate and the population-based nature of the study we were able to avoid overestimation of adverse outcome that is a common feature in clinical materials. A total of 0,4% of Norwegian children in 2002 did not attend general public schools (127). Youth with a very active and severe epilepsy, including severe intellectual disability, will not have been included in the study as they did not attend ordinary schools. Of eligible participants, 15% did not answer the questionnaires. We know little about this group, but we know that people with severe epilepsy tend to suffer in terms of school attendance (80). If there is a higher frequency of pupils with active epilepsy among non-participants, this will serve as a selection bias. Thus, it may be assumed that our findings would be even more profound had all adolescents with epilepsy been included.

Recall bias

Recall bias appears when case- and control groups have a different recollection of events. This may be due to different awareness on a certain topic between participants. WVE may previously have been aware of a link between epilepsy and eating disorders, and thus be more likely to report symptoms of eating disorders than others. Collection of our material was finished in 2008, and such awareness may not have been clear at that time. Although our material in MoBa for the most part is prospective, some variables will have been retrospective, and in retrospective data there is a possibility for inaccuracy in recalled information. Retrospective information of weight prepregnancy was used. The questions about eating disorders in MoBa are retrospective and this method of self-reporting is prone to recall bias. Direct

interviews might have yielded more precise diagnostic information both in terms of eating disorders, and in terms of the epilepsy diagnosis.

In the Health Profile for Children and Youth in Akershus study the issue with retrospective recollection of events is more prominent. Retrospective dietary information is generally hard to remember, and recall accuracy may also be different among groups. Young people with eating disorders are more likely to be aware and focused on diet, and will be more likely to remember accurately.

The diagnosis of epilepsy may also be influenced by uncertain recollection or general uncertainty about diagnosis. A limitation in both materials used is little clinical information about type of epilepsy, diagnostic features and certainty of diagnosis. A follow-up study of MoBa has been conducted with the purpose to validate the diagnosis of epilepsy (128). All MoBa participants were sent follow-up questionnaires regarding complementary information about epilepsy diagnosis and AED-use. Hospital records of MoBa participants residing in Western Norway (n=40) were examined to further clarify epilepsy diagnosis, and blood samples collected in MoBa were examined for AED-detection (128). Half of the 300 women returned the questionnaire and 98% of these women confirmed a diagnosis of epilepsy. When comparing hospital records for women in Western Norway, the epilepsy diagnosis was confirmed in 95% of cases. This validation used the previous definition of epilepsy, and not the current definition described in chapter 1.1. Similarly, AED-use was detected in 95% of the cases where a mother had reported using AED. In conclusion, the reported epilepsy diagnosis in MoBa was in general confirmed by the validation studies.

Channeling bias

When drugs of similar indications are prescribed to a group of patients with different prognostic factors, it is called channeling bias (129). In our MoBa material this will be a probable bias, especially in women who use lamotrigine. Lamotrigine is also

used as a mood stabilizer and neurologists may have an inclination to prescribe this particular drug to women with psychiatric symptoms, and this could be a factor when considering the high risk of severe peripartum depression and/or anxiety in overweight women using lamotrigine.

Missing data

Missing data was a substantial challenge in collecting our data. Information about ED was only available for 73,171 pregnancies in MoBa. This means that close to 30% of women did not answer one or more questions about ED in the questionnaires. This will increase the possibility of bias, especially selection bias, as we do not know the characteristics of the women who had missing data. A way to offset missing data is by imputation, a statistical method to reduce the effects of missing data. When imputating data there is a risk of losing precision. We did not impute for any data in our three papers, because we did not want to lose precision in an outcome variable.

5.1.3 Confounding

When investigating the causal effect of variable a to variable b , in example if epilepsy by itself causes overweight, it is important to be aware of the possibility of a variable c that influences both a and b ; a confounder.

A confounder is defined the following criteria (130):

- A confounder must influence the outcome by a different pathway than the studied exposure.
- The confounder cannot be an intermediary in the causal pathway between exposure and outcome.
- The confounder must be associated with the studied exposure.

For epilepsy and overweight multiple confounders were considered, such as education and family economy. Using MoBa we were able to adjust for these variables in our

logistic regression model, and as a result minimize the effect of confounding factors. We also adjusted for smoking, parity and being a single parent. In the Health Profile for Children and Youth in Akershus study, we were able to adjust for smoking and perception of family economy, using logistic regression.

Although multiple confounders were adjusted for, there is a possibility of hidden, additional confounders. Hidden confounders are variables that are either not known or variables that are unavailable for statistical adjustment, the latter called unmeasured confounders.

Especially in studying youth with epilepsy from Akershus, we would have preferred to have more socioeconomic data to account for. Self-reported perception of family economy is a subjective measure of socioeconomic status and may not reflect true values. We would have liked to be able to adjust for family structure, parents' educational level and family income, as these are known confounders and valid measures of socioeconomic status.

By adjusting for confounders in statistical models we were able to obtain better measure of true group-level differences, and as such increase specificity. Although specificity increases, there is a possibility that sensitivity decreases by using this method. Methods should be chosen to balance sensitivity and specificity in an optimal way.

It is important to differentiate between mediators and confounders (see the definition of a confounder, second criterion). An example in our study is the use of AED. AED in some cases increases weight and thus works as an intermediary between the causal effect of epilepsy (exposure) and overweight (outcome). We acknowledged this by comparing WWE with and without use of AED, "stratification". We also compared the effect of different subgroups of AEDs, but statistical power was a challenge for the majority of such subgroups due to small numbers.

A challenge we have been aware of in our studies is collinearity. This is when two variables are highly correlated and this leads to difficulty in statistically separating effects of these variables, meaning effect-estimates will be unstable (124). When comparing variables, and when adjusting for specific socioeconomic variables, we have tried to avoid this potential pitfall.

When adjusting for confounders there needs to be an awareness of the possibility of overfitting. This is a statistical phenomenon that can occur when the ratio of the number of adjusting factors to the number of events is less than 1:10 in a logistic regression model (131). Overfitting will lead to inflated effect estimates. In some of the comparisons in our work, for example studying overweight women using lamotrigine, we cannot exclude the possibility that effects estimates is exaggerated due to overfitting. However, we do not find it likely, as the crude estimates was very similar to the adjusted estimates.

5.1.4 External validity

External validity refers to the generalizability of the study population. To which degree can we transfer associations in the study population to the general population? MoBa is a population based cohort study. Population based cohort studies covers people from all parts of society, and in our case from all over the country. This increases the study's generalizability. A large study population also increases generalizability. In cohort studies a specific characteristic is often included to get a representative study population (132). In MoBa, only pregnant women were included. This makes it difficult to make generalizing conclusions beyond the target population.

The Health Profile for Children and Youth in Akershus study is a cross sectional study with a large number of participants. Its external validity is good due to a very high response rate of 85%. This was due to the study design where children and adolescents gave their contribution during school hours and in the class-room. Randomization of chosen school classes were performed and, due to the Norwegian

school system with more than 96% of children attending state funded schools, a representative selection was obtained.

Consistent findings in two different study populations, such as increased risk of eating disorders among people with epilepsy both in MoBa and the Health Profile study, also increases external validity.

5.1.5 Errors

Random errors can occur during inclusion, registration and analysis. Level of precision Confidence intervals (CI) mirrors the level of precision of results. A wide CI means low precision, and precision increases as CIs narrows. A way to reduce the influence of random errors is to increase the study population. In our materials we have large study populations, but for analysis of small subgroups there is a possibility that random errors influence results. One example is analysis of lamotrigine users with overweight in MoBa (n=38), where it is possible that random errors could have influenced risk estimates in pregnancy for this group.

5.2 Discussion of results

5.2.1 Epilepsy and eating disorders

In our material from the Health Profile for Children and Youth in Akershus Study, we found that youth with epilepsy more often than others were seeking help of health personnel for eating disorders. Tegethoff et al studied the temporal associations between mental disorders and physical diseases in adolescents (13-18 years) with mental-physical comorbidities in a nationally representative United States cohort (133). They found a significant association between epilepsy and any eating disorder (HR 6.27, CI 1.58-24.96). In that study, diagnoses were self-reported. It is

hypothesized that an association between epilepsy and eating disorders arises from a right hemispheric focus and right frontal intracerebral lesions because of their close relationship to the limbic system (134). This is based on case-reports where eating disorders in patients with epilepsy resolved after right temporal lobe lesions (134).

We found an increased risk of eating disorders also among pregnant WWE. We were able to distinguish between the different types of eating disorders due to the questions in MoBa covering diagnostic criteria from DSM-IV. The most frequent eating disorder among WWE was weight inducing types such as binge eating disorder, but also the outcome of impaired bodyimage was significantly increased in the epilepsy group. As described in methods this is a variable containing questions mirroring diagnostic elements in anorexia nervosa, but criteria of amenorrhea and low BMI was left out. The study population will not have low-weight induced amenorrhea as they are pregnant women, nor is low BMI compatible with pregnancy. An edited version of these criteria was therefore necessary to get an impression of mental health challenges in a population of pregnant women. This is in line with previous studies of eating disorders in MoBa (111).

The results of two similar variables in the two different materials, impaired body image in MoBa and satisfaction with looks in Health Profile, are coinciding. This means that a negative personal image in people with epilepsy debuts early, at least in adolescents, and continues later in life. A negative personal image, or bodyimage, is the root of developing an eating disorder. We would hypothesize that stigma plays a part in the early development of impaired selfworth in people with epilepsy. An individual exposed to stigma will feel as an outsider or less normal. Striving to be normal, body appearance is easier to control or change than perhaps the epilepsy diagnosis is, and therefore youth and adults will be at risk of developing an eating disorder.

Recommendations to screen school aged youth with active epilepsy for difficulties in school achievement (80) and for psychiatric comorbidity such as depression and anxiety (78) is a clear recommendation. Screening is a tool to be used to relocate

resources to children and adolescents in need of extra care. However, it is important to locate resources to this task in clinical departments, as time shortage may render doctors unable to fulfill the recommendation. Systematically organizing for example epilepsy nurses to undertake screening for these disorders, may be a solution. A similar approach should be taken in dealing with eating disorders, both in youth, but also later in life, as our study reveals that this is a frequent challenge for people with epilepsy.

5.2.2 Epilepsy and overweight

We found that WWE are more overweight than other women without epilepsy. Several AEDs are weight inducing, such as valproate, carbamazepine, and pregabalin (92).

Valproate is weight inducing in patients on such drug treatment for either epilepsy or migraine (135-137), ranging from an average 2.0 kg weight increase after one year to an increase of 5.8 kg after 32 weeks. Lamotrigine is considered to be weight neutral (136, 138).

We have found that WWE and overweight have an increased risk of pregnancy complications, as well as an increased risk of poor outcome for the child. This risk was increased compared to normal-weight women without epilepsy, but also compared to normal-weight WWE, and compared to overweight women without epilepsy. When AEDs are prescribed to fertile WWE weight-gain and overweight should always be considered.

The association between AED use and overweight in our study was modest, and this suggests that the observed increase in BMI was mediated by other factors as well. As discussed in the previous chapter, the eating disorder with the highest frequency in WWE was binge eating. This is a weight inducing eating disorder, and could play a part in the increased BMI in the epilepsy group.

We found no difference in BMI when comparing adolescents with epilepsy to adolescents without epilepsy. However, we found that youth with epilepsy were more prone to have an unhealthy diet, meaning daily consumption of candy, sugar-containing soda, potato chips, or French fries than the controls. It was therefore rather surprising that overweight did not occur with an increased frequency in the epilepsy-group.

Previous studies have found an association between epilepsy and overweight. One study found an association between obesity, idiopathic generalized epilepsy and family history of epilepsy in a population recruited from an adult epilepsy clinic (139). In another study, the epilepsy group participated less in physical activities and had a higher BMI, supporting that overweight in epilepsy at least in some part is caused by lifestyle (98). In our material of youth in Akershus, youth with epilepsy were found to be as active as the reference group. Neither did the epilepsy group have more overweight, thus underlining the theory that these two factors are associated. We were not able to study physical activity in MoBa. It is possible that physical activity decreases in the epilepsy group when they become adults, when organized sport-activities in school are no longer available. Physical activity could therefore be a mitigating factor in nullifying other risk factors such as unhealthy diet, use of AED and weight inducing eating disorders.

Previously people with epilepsy have been discouraged to participate in physical activities (65), and this recommendation may have lead to less exercise and increased rates of overweight in this group. In a Norwegian study of outclinic patients, exercise was reported as a possible precipitant of seizures in 10% of cases. The majority of patients had no adverse effect of training, and a third reported that physical exercise contributed to improved seizure control (65). Exercise should be encouraged for people with epilepsy, as well as for the population as a whole. Physical activity has during pregnancy been found to have a positive effect on birth outcome as low perinatal mortality was seen in those performing recreational physical activity at least

once a week (140), supporting a recommendation of physical activity also in pregnant WWE.

Overweight/obesity is a significant secondary health problem in youth with intellectual disability and adolescents with intellectual disability is at a higher risk of being overweight/obese than their peers (141). This is also evident in adult populations (142). Cognitive impairment is more frequent in patients with epilepsy than in a population without epilepsy, and this may be another contributing factor to overweight in epilepsy.

5.2.3 Epilepsy and outcome for pregnancy and delivery

We have found that overweight is a significant contributing factor for the increased risk of pregnancy complications in WWE, as WWE and overweight have more complications than both normal weight WWE, and overweight women without epilepsy. Epilepsy is a known risk factor for complications during pregnancy and delivery, and for child outcome (42, 44, 45, 52, 53, 57, 66). Mechanisms behind these findings are scarcely studied, and risk stratification is needed. Overweight is important as it is a modifiable factor.

For some of the variables tested, epilepsy and overweight had additive effects on several outcomes, including caesarean section, excessive bleeding during delivery, and transfer to a neonatal ward. Caesarean section is increased in most chronic diseases (143). In regards to epilepsy there is an indication for caesarean section if seizures occur during labor, or the patient is unable to cooperate due to sedation (144). In hypertensive disorders, such as preeclampsia, elective caesarean section is a frequent mode of delivery (145). In our material, preeclampsia rates were increased in women having a caesarean section, and both with and without epilepsy. This could therefore have been an indication for caesarean section in both groups. Preeclampsia

alone cannot alone explain the full effect overweight had on rates of caesarean section in WWE.

We stratified our material so that we were able to compare WWE using AEDs to those who did not. AED use had an effect on risk of excessive bleeding, transfer of the child to a neonatal ward, and having small for gestational age children. Vitamin K supplements before birth are often given to women using enzyme-inducing AED such as carbamazepine and phenytoin to avoid bleeding (45). AED can also cause excessive bleeding due to uterine atony (45). In our study an increased risk of bleeding during delivery was seen for overweight women using AED compared to other overweight women, but not compared to normal weight WWE without AED. This implies AED use could be a causative factor for bleeding.

Overweight women using lamotrigine had increased odds ratios for several complications (figure 5). Lamotrigine users with overweight was a relative small group, containing just 38 individuals in that study, and thus the statistical power is low with wide confidence intervals. Lamotrigine is also used for psychiatric diagnoses such as depression and anxiety. This could be a source for channelling bias, where physicians are more prone to prescribe lamotrigine to WWE and comorbid psychiatric disease. This will increase the proportion of psychiatric challenges in the lamotrigine group, and again lead to variables such as caesarean section and neonatal transfer being more frequent in this group. However, lamotrigine is often the drug of choice in pregnancy, and all overweight women using lamotrigine need to be carefully monitored.

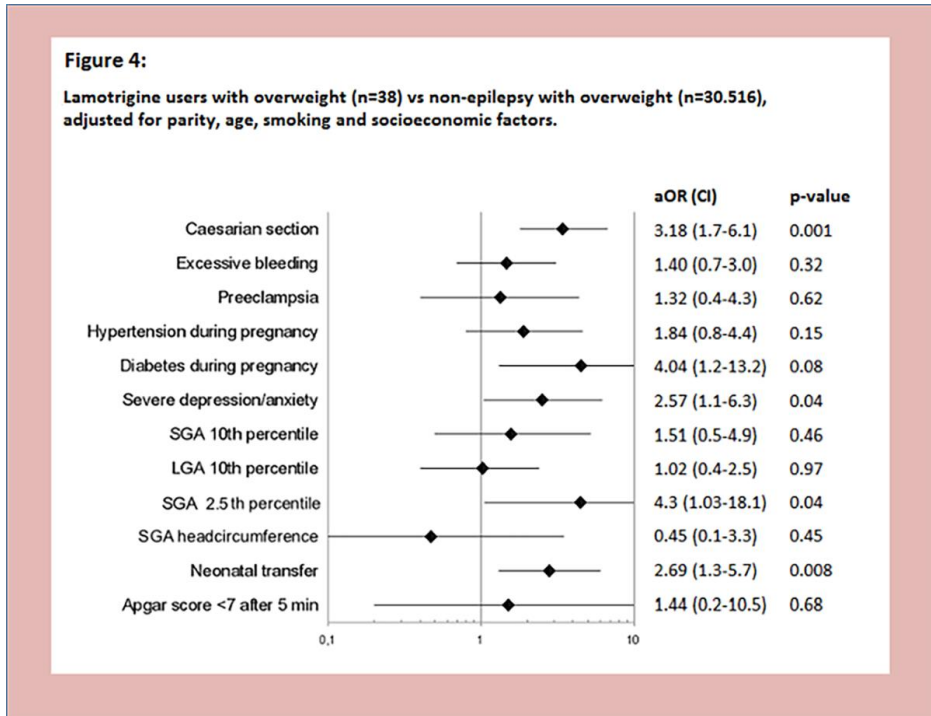


Figure 5: Lamotrigine users with overweight at risk, from (146).

Overweight in mothers with epilepsy is a risk factor for several obstetrical complications. An interesting outcome which we so far have not been able to study is overweight in mothers as a risk factor for epilepsy in the offspring. Razaz and coworkers recently published a paper where they used two large population based registers in Sweden (Sweden Medical Birth Register and National Patient Register). More than 1.4 million children were included in the study and 7592 (0.5%) were diagnosed with epilepsy. They found that rates of childhood epilepsy increased with maternal overweight or obesity in a dose-response manner (147). The authors hypothesize that obesity-induced inflammation affects neurodevelopment in the foetus and that this could be a mechanism for epilepsy in the child. Another theory is that mothers with overweight have a greater risk of pregnancy-associated diseases such as hypertensive disorders and diabetes, and that this may contribute to epilepsy in the

child. Maternal epilepsy is a risk factor for epilepsy in the child also as a genetic heritability (148). It is very interesting that also maternal environmental factors seem to have an effect.

5.3 Conclusions

Overweight are more frequent in pregnant WWE compared to women without epilepsy. The combination of overweight and epilepsy exposes mother and child to a significantly increased risk of complications during pregnancy and in the perinatal period. Therefore, overweight WWE should be considered as a high-risk group during pregnancy and should be monitored closely in terms of mental health, symptoms of preeclampsia, diabetes, and intrauterine growth restriction. Referral to a nutritionist should be considered for WWE, both when AED treatment is started and when planning a pregnancy.

Eating disorders are frequent in youth with epilepsy, and also in pregnant WWE. This is especially valid for weight-inducing eating disorders and underlines the importance of intervention with nutritionists and increasing awareness of health issues linked to overweight in epilepsy.

5.4 Importance and outcome of research

Our findings in this study have been incorporated into the new national guidelines for epilepsy treatment and follow-up (149). Information about the increased risk of complications during pregnancy for overweight WWE have been included in an information folder produced by the Norwegian Epilepsy Patient Organisation (150). Both papers on pregnant women was also cited in a recent authoritative review paper on women with epilepsy published in *Lancet Neurology* (151).

5.5 Future directions

Future research is still needed on this topic. How do the individual antiepileptic drugs influence pregnancy and delivery? To what degree do they cause overweight? People with epilepsy is a heterogenic group, and how do epilepsy-types differentiate in terms of comorbidity? A register with better information about what kind of epilepsy each participant have is integral to better stratification and investigation of subgroups. A register is also important to ensure the prospective nature of research in the field of pregnancy among WWE where women would be included in the register before they become pregnant. In Bergen, the recently started project EPI-REG, has set aim to fulfil this. Questionnaires in EPI-REG has partially been designed on the back of results from research performed in Bergen Epilepsy Research Group (BERG), and also due to results presented in this thesis. An emphasize has been put on noting BMI and questions have been designed to monitor mental health, included signs of eating disorders.

We are also using EPI-REG to build a large bio-bank including a large set of blood samples. We have also approval for inclusion of placenta biopsies from women with epilepsy harvested after delivery. This will enable research in genetics in people with epilepsy, but perhaps more exciting studies of epigenetics and gene-environment interactions in relation to epilepsy and comorbidities.

Another way of increasing statistical power is to merge registers. This leads to a higher number of participants and high statistical power, but also generate better opportunities for stratification and investigation of subgroups, in example subgroups of people using different antiepileptic drugs. SCAN-AED (www.SCANAED.org) is a new initiative from BERG where information on all births in the Nordic countries the last 15 years are included to study health consequences of AED exposure during pregnancy. Health registers (the birth registers, prescription databases, hospital registers and cancer registers) are linked with socioeconomic data from the National

Statistical agencies in Norway, Sweden, Denmark, Iceland and Finland. The data are linked on the individual level, and the linked files are pooled to one file to enable sophisticated regression models. The population encompasses about 4.5 million births where more than 20.000 have been exposed to AED. There are more than 4500 births exposed to lamotrigine. As all the medical birth registers in the Nordic countries include information on maternal BMI, it will be possible to study the combined risk of lamotrigine and overweight on pregnancy outcome in detail.

Another possibility to increase number of participants is to combine MoBa data with data from The Danish National Birth Cohort which is the Danish equivalent to MoBa. This is currently just at a planning stage, but could be a focus point for BERG in the future.

There are still a lot of unknown variables and uncertainties in epilepsy. As I have pointed out in this thesis there are challenges in everyday treatment and interaction with people with epilepsy, and epilepsy is still a huge challenge in terms of future research. This should inspire further work in this field to potentially better lives and make people master living comfortably with an epilepsy-diagnosis.

Source of data

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6. Original publications

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Kolstad E, Bjørk M, Gilhus NE, Alfstad K, Clench-Aas J, Lossius M. (2017): "Young people with epilepsy have an increased risk of eating disorder and poor quality diet", *Epilepsia Open*



Short Communication

Epilepsy and eating disorders during pregnancy: Prevalence, complications and birth outcome

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ABSTRACT

Purpose: The aim was to investigate the prevalence of eating disorders and its relation to pregnancy and delivery complications in childbearing women with epilepsy (WWE).

Method: This study is based on The Norwegian Mother and Child Cohort Study (MoBa) linked to the Medical Birth Registry of Norway. Epilepsy was reported in 706 pregnancies. The remaining cohort ($n = 106,511$) served as the reference group. Eating disorders were diagnosed using DSM-IV criteria adjusted for pregnancy. The risk of preeclampsia, gestational hypertension, diabetes and weight gain during pregnancy as well as delivery outcome (small for gestational age, large for gestational age, ponderal index, low APGAR score, small head circumference) were calculated as odds ratios (ORs) with 95% confidence intervals (CIs) adjusted for maternal age, smoking, parity and socioeconomic factors.

Results: Pregnant WWE were significantly more likely to have binge eating disorder (6.5% vs. 4.7%, $p < 0.05$). WWE and comorbid eating disorders had significantly more preeclampsia (7.9% vs. 3.7%, $p < 0.05$), peripartum depression and/or anxiety (40.4% vs. 17.8%, $p < 0.001$) and operative delivery (38.2% vs. 23.5%, $p < 0.001$) than the reference group without epilepsy or eating disorders. After adjustment for confounders, a significantly increased risk of operative delivery (OR 1.96, CI 1.26–3.05) and peripartum depression and/or anxiety (OR 2.17, CI 1.40–3.36) was demonstrated.

Conclusion: Eating disorders in WWE contribute to the increased risk of pregnancy and delivery complications. Health personnel should be aware of eating disorders in WWE and refer them for treatment before pregnancy.

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1. Introduction

Antiepileptic drug (AED) treatment is used by 0.2–0.7% of pregnant women [1,2]. Several obstetrical complications such as preeclampsia, gestational hypertension, caesarian delivery, congenital malformations and low birth weight occur more frequently in these women than in women without epilepsy [3]. Adverse birth outcomes in women with epilepsy (WWE) are believed to be

mediated by AED use, although the exact mechanisms of action and the role of confounding factors remain unclear. Comorbid eating disorders (ED) are an unexplored potential contributor to pregnancy complications in WWE.

Using data from The Norwegian Mother and Child Cohort Study (MoBa), Reiter et al. [4] found an increased life time prevalence of self-reported, unspecified ED in pregnant WWE. Rai et al. also found an increased frequency of ED (OR 2.9) in non-pregnant persons with epilepsy [5].

Adverse pregnancy outcomes are more frequent in women with ED, especially for the subgroup with binge eating disorder (BED) [6]. Women with BED deliver babies that are large for gestational age and have an increased risk of caesarian section. An increased rate of miscarriages has been noted in both anorexia nervosa (AN)

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and bulimia nervosa (BN) [7,8]. ED have also been linked to an increased risk of stillbirth, low birth weight, low Apgar scores, breech presentation, lower weight-for-length offspring trajectories and cleft lip and palate [9,6,10].

As both epilepsy and ED increase the risk of complications during pregnancy and delivery, we investigated the prevalence and subtypes of this combination during pregnancy, and estimated possible impacts of ED in epilepsy on pregnancy and birth outcome in WWE.

2. Materials and methods

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999 to 2008. The women consented to participation in 40.6% of the pregnancies. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. The response rate was 45% [11]. The women received standardized questionnaires addressing information on maternal epilepsy, psychiatric symptoms and socioeconomic status. The MoBa database is linked to the Medical Birth Registry of Norway that contains information on pregnancy and delivery complications.

The MoBa database comprises 706 pregnancies in women with epilepsy and 106,508 pregnancies in women without epilepsy. Information concerning ED was available for 73,171 pregnancies. The MoBa epilepsy cohort has been validated [12,13].

The women answered questions in accordance with DSM-IV criteria for AN, BN and BED. The questions were slightly adjusted due to the cohort being pregnant, amenorrhea was not required in AN. We also evaluated "impaired bodyimage" defined as fulfilling the AN criteria, except for amenorrhea and low BMI criteria. The frequency of fasting, use of laxantia and vomiting during pregnancy was investigated. The rates of ED in the women without epilepsy in the MoBa study have been validated [14].

We investigated the relationship between epilepsy and any type of ED (except for impaired body image) and hypertension during pregnancy, diabetes during pregnancy, preeclampsia, peripartum depression and/or anxiety [15], excessive pregnancy weight gain (>16 kg), operative deliveries (caesarian section, use of vacuum or forceps), small for gestational age (<10th percentile), large for gestational age (>10th percentile), small head circumference (<10th percentile) [16], low Apgar score (<7 after 5 min) and

ponderal index (weight/length³, <10th percentile and >90th percentile). Neonatologists have preferentially used the ponderal index rather than small for gestational age as an indicator of nutritional status in the child, and the variable is a predictor of neonatal disease [17].

IBM SPSS Statistics version 21 was used. We investigated group differences using Student's *t* test and Pearson's χ^2 test (Fisher's exact test if any cross table cell had an expected count < 5). Binary logistic regression was used to estimate the odds ratio (OR) with 95% confidence interval (CI) for pregnancy and delivery complications adjusted for the confounding factors maternal age, parity, smoking and socioeconomic factors (low household income, low education or being a single mother).

The study was approved by the Regional Ethical Committee in Western Norway.

3. Results

WWE in the MoBa cohort more frequently had lower educational attainment, low income, single parenting, and were younger than women without epilepsy [15]. They also had significantly higher weight and BMI than the reference group (Table 1).

There was a significantly increased rate of BED and "impaired body image" during pregnancy in WWE compared to women without epilepsy (Table 1). "Impaired body image" was significantly increased in both women using AED monotherapy (6.9%, $p < 0.05$, $n = 266$) and polytherapy (9.4%, $p < 0.05$, $n = 72$), as compared with the reference group (3.6%). No difference in prevalence was found for bulimia or anorexia before or during pregnancy.

WWE and comorbid ED had significantly more often preeclampsia (7.9% vs. 3.7%), peripartum depression and/or anxiety (40.4% vs. 17.8%) and operative delivery (38.2% vs. 23.5%) than women without epilepsy and no ED (Fig. 1). WWE and comorbid ED had more peripartum depression and/or anxiety than WWE without ED (40.4% vs. 24.2%, $p < 0.01$). No confounding factors were considered in this analysis.

After adjusting for confounding factors, WWE and comorbid ED had a significantly greater risk of peripartum depression and/or anxiety (OR = 2.17, CI 1.4–3.4, $p < 0.001$) and operative delivery (OR = 1.96, CI 1.3–3.0, $p < 0.01$, Fig. 2). After additional adjustment for AED use, the risk of operative delivery was no longer significantly higher (OR 1.35, CI 0.7–2.5, $p < 0.35$).

Table 1
Weight, BMI and eating disorders in women with and without epilepsy.

	Reference <i>n</i> = 106,508	Epilepsy <i>n</i> = 706	No AED ^b <i>n</i> = 367	AED <i>n</i> = 338
Weight (SD)	68.0 (12.9)	69.5 (13.7)**	69.2 (13.0)*	69.7 (14.3)*
BMI (SD)	24.0 (4.3)	24.7 (4.6)***	24.6 (4.5)	24.8 (4.8)
Impaired bodyimage ^c	2356 (3.6%)	30 (6.1%)**	13 (4.9%)	17 (5.3%)*
BED ^a pre-pregnancy ^f	3165 (3.3%)	30 (4.5%)	13 (3.7%)	17 (5.3%)*
BED during pregnancy ^d	4298 (4.7%)	41 (6.5%)*	21 (6.3%)	20 (6.6%)
Bulimia pre-pregnancy ^e	1747 (1.7%)	7 (1.0%)	4 (1.1%)	3 (0.9%)
Bulimia during pregnancy ^d	466 (0.5%)	1 (0.1%)	1 (0.3%)	0 (0%)
Use of laxantia during pregnancy ^{d,f}	79 (0.1%)	0	0	0
Fasting during pregnancy ^{d,f}	60 (0.1%)	2 (0.3%)*	1 (0.3%)	1 (0.3%)
Vomiting during pregnancy ^{d,f}	392 (0.4%)	4 (0.7%)	2 (0.7%)	2 (0.6%)

^a BED = binge eating disorder.

^b AED = antiepileptic drugs.

^c Pre-pregnancy = last 6 months before pregnancy.

^d During pregnancy = gestation week 17–19.

^e Impaired bodyimage = DSM-IV criteria for anorexia nervosa, but amenorrhea and BMI < 18.5 were not required.

^f Use of laxantia, fasting or vomiting at least once a week with the purpose of controlling body weight.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs. the reference group.

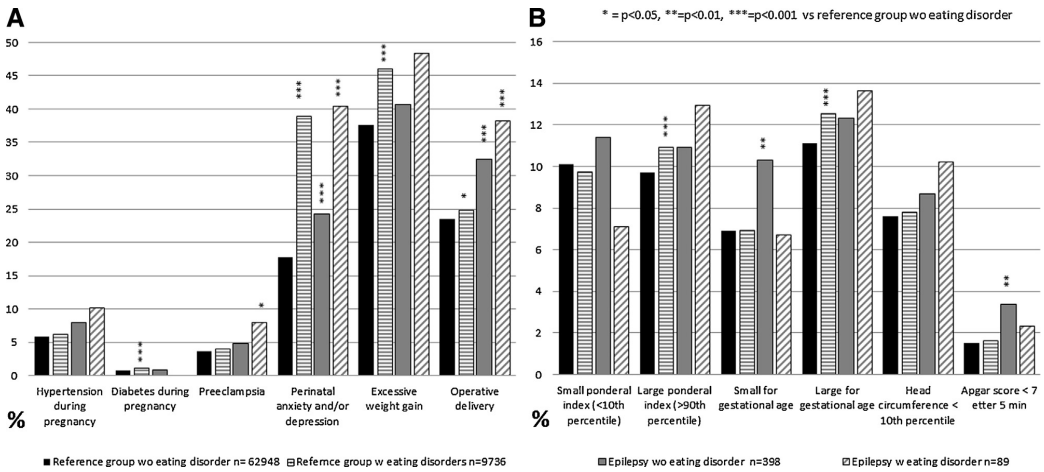


Fig. 1. Pregnancy and delivery complications (plot A) and birth outcome (plot B) according to a diagnosis of epilepsy and/or eating disorders. Significance levels are marked with *, compared with the reference group without eating disorder. W = with, wo = without.

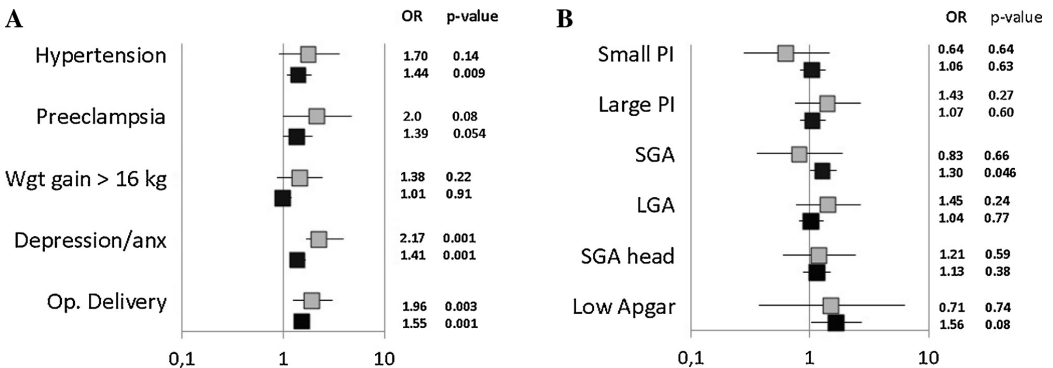


Fig. 2. Complications during pregnancy, delivery and birth outcome. WWE and ED (grey markers) and WWE and no ED (black markers) compared with the reference group (all other women in MoBa). Risk of complications during pregnancy (plot A) and risk of adverse birth outcome (plot B). The estimates are adjusted for parity, maternal age, smoking and socioeconomic factors. Depression/anx = peripartum depression and/or anxiety. Op. delivery = caesarian section, use of vacuum or forceps. PI = ponderal index. SGA/LGA = small/large for gestational age. SGA head = small for gestational age head circumference. Low Apgar: <7 after 5 min.

4. Discussion

Pregnant WWE have an increased risk of binge eating disorder. WWE and comorbid ED more often had operative deliveries and pregnancy related depression and/or anxiety.

In contrast with other psychiatric disorders, ED has rarely been studied in epilepsy. Using DSM-IV criteria we found slightly higher rates of ED than reported in non-pregnant patients with epilepsy (5% point prevalence) [5]. Possibly, earlier estimates of ED in epilepsy did not include BED. In women without epilepsy, BED is the most common type of ED during pregnancy [18]. As reproductive health is negatively affected by ED [19], a lower rate of ED in pregnant than in non-pregnant WWE is expected. This is supported by Reiter et al. who found an increased life-time prevalence of unspecified self-reported ED in pregnant WWE compared with other women in the same study sample (4.8% vs. 2.9%), but very few reported having such disorders during pregnancy (0.4% vs. 0.3%). Similarly, unspecified ED

has been found in only 0.8% of women without epilepsy after delivery [20].

The subgroup of WWE with ED had a numerically higher risk than the rest of the epilepsy cohort for the majority of pregnancy and delivery complications investigated. However, the power to find an ED related difference surpassed 60% only for peripartum depression and/or anxiety as well as operative deliveries. Our results were probably driven by BED. This disorder increases the risk for complications during pregnancy and delivery, and adverse birth outcome, such as higher birth weight babies, higher risk of large for gestational age and caesarian section than the referent [6].

There are several explanations as to why WWE with ED have more pregnancy complications. Women with ED are more likely to smoke during pregnancy [18]; this is why we adjusted for this in our binary logistic regression model. Comorbid anxiety, depression and excessive weight gain may be associated with adverse effects on pregnancies and birth outcome [21,22]. Furthermore, the use of AEDs is a risk factor for pregnancy complications [3,12], and partly

mediated the risk for operative deliveries in WWE and ED in our data.

The prospective design of the MoBa study minimized reporting bias. The participation rate of 40.6% at first assessment is expected for population-based studies [23]. A study investigating selection bias found that epilepsy prevalence was similar in the MoBa study and in the general Norwegian population [24].

5. Conclusion

The increased risk for complications in WWE with ED during pregnancy with possible adverse health effects for both mother and child should be considered and minimized in consultations both before and during pregnancy.

Conflict of interest statement

Eivind Kolstad has no conflicts of interest. Marte Helene Bjørk and Gyri Veiby have received lecture honoraria from Glaxo Smith Kline and congress travel support from UCB pharma. N.E. Gilhus has received lecture fee from Octapharma, Baxter, and Merck Serono.

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Overweight in epilepsy as a risk factor for pregnancy and delivery complications

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SUMMARY

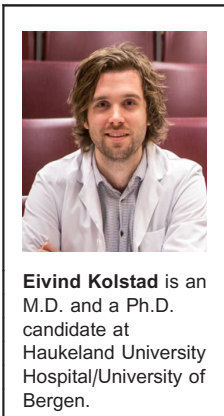
Objective: To investigate whether prepregnancy overweight in women with epilepsy increases their risk for complications during pregnancy and delivery.

Methods: This study is based on The Norwegian Mother and Child Cohort Study (MoBa) linked to the Medical Birth Registry of Norway. A diagnosis of epilepsy was reported in 706 pregnancies. Overweight was defined as body mass index ≥ 25 prepregnancy. Overweight women with epilepsy ($n = 259$) were compared to normal-weight women with epilepsy ($n = 416$), and to women without epilepsy with and without overweight ($n = 30,516$ and $n = 67,977$, respectively). The risks of pregnancy and delivery complications were calculated as odds ratios (ORs) with 95% confidence intervals (CIs) adjusted for adverse socioeconomic factors, age, parity, and smoking.

Results: Women with epilepsy were more often overweight than women without epilepsy (38.4% vs. 31.3%, $p < 0.001$). The majority of pregnancy and delivery complications were more frequent in overweight women with epilepsy. Compared to overweight women without epilepsy, the risk was increased for cesarean section (OR 1.6, CI 1.2–2.2, $p < 0.001$), excessive bleeding (OR 1.4, CI 1.0–1.8, $p = 0.04$), peripartum anxiety and depressive symptoms (OR 1.9, CI 1.3–2.8, $p < 0.001$), small for gestational age children (OR 2.4, CI 1.2–4.8, $p = 0.02$), and transfer of the infant to a neonatal ward (OR 1.5, CI 1.1–2.2, $p = 0.02$). Compared to normal-weight women with epilepsy, the risk of cesarean section (OR 1.6, CI 1.1–2.3, $p < 0.05$), gestational hypertension (OR 2.0, CI 1.1–3.5, $p < 0.05$), preeclampsia (OR 2.3, CI 1.2–4.5, $p < 0.05$), and transfer of the infant to a neonatal ward (OR 2.2, CI 1.3–3.6, $p < 0.01$) was increased.

Significance: Prepregnancy overweight in combination with epilepsy entails a strong negative effect on risk of complications during pregnancy and delivery. In women with epilepsy and overweight referral to a nutritionist should be considered when an antiepileptic drug is started as well as when pregnancy is planned. These women should be regarded as a high-risk group.

KEY WORDS: The Norwegian Mother and Child Cohort Study, Epilepsy, Overweight, Obesity, Pregnancy.



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Women with epilepsy are a vulnerable group, especially during pregnancy. Obstetric complications such as depression, anxiety, preeclampsia, gestational hypertension,

cesarean delivery, congenital malformations, and low birth weight are reported more frequently than in women without epilepsy.^{1–3} Most studies have not been adjusted for overweight, even though overweight and obesity are known causes of complications during pregnancy and delivery, as well as of adverse birth outcome. Conditions such as preeclampsia, diabetes during pregnancy, fetal macrosomia, stillbirth, perinatal death, and postterm pregnancy are all known to be more frequent in overweight and/or obese women.^{4,5} Obese women are more likely to experience antenatal and postpartum depression symptoms, with a

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KEY POINTS

- Women with epilepsy are often overweight
- Overweight and epilepsy represent additive risks for cesarean section, bleeding complications, and neonatal transfer
- Overweight women with epilepsy should be regarded as a high-risk group during pregnancy and be followed closely
- Referral to a nutritionist should be considered for women with epilepsy

moderate increased risk also for overweight women.⁶ Antiepileptic drugs (AEDs) are known to influence body weight.⁷ AEDs associated with weight gain are gabapentin, pregabalin, valproate, vigabatrin, and possibly carbamazepine. AEDs associated with weight loss are felbamate, topiramate, and zonisamide. Lamotrigine, levetiracetam, and phenytoin are believed to be weight neutral.⁷ It is unknown whether AEDs have any additional effects on weight control in pregnancy.

Our first aim was to establish the frequency of overweight and obesity in women with epilepsy. The effect of overweight on complication risk during pregnancy and delivery has not been investigated in women with epilepsy. Our second aim was to compare overweight women with epilepsy to overweight women without epilepsy, as well as to normal-weight women with and without epilepsy, to determine to what degree overweight contributes to the increased complication rate in epilepsy. Because both overweight and epilepsy represent known risk factors for pregnancy and delivery complications, we wanted to explore the combined effect of these two factors to see if they had an additive or potentiating effect on the outcome.

MATERIALS AND METHODS

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.^{8,9} Participants were recruited from all over Norway from 1999 to 2008. The women consented to participation in 41% of all invited pregnancies. The current study includes 107,516 pregnancies, where epilepsy was reported in 713 cases. Women answered the following question in week 17–19 of pregnancy when they were included in the study: Do you have or have you had epilepsy? They were also instructed to provide information about any medication taken in conjunction with the illness. Diagnosis of epilepsy and AED use in MoBa has been validated with further retrospective questionnaires, by AED plasma measurements as well as investigation of hospital records on patients from Western

Norway.¹⁰ The dataset was also linked to the Medical Birth Registry of Norway (MBRN), a national health registry containing information on all births in Norway during the study period. The attending physician or midwife collects medical information during delivery for all births after 12 weeks of gestation, including information on epilepsy and AED intake. The retrospective questionnaires confirmed the epilepsy diagnosis in all but seven women. The examination of patient journals confirmed the epilepsy diagnosis in 95% when applying the International League Against Epilepsy (ILAE) criteria.^{11,12} With the help of blood samples from the MoBa Biobank, the detection rate of AEDs in blood of women who reported taking such drugs was 95%. This leads to a positive predictive value (PPV) of 98.8% and a specificity of 99.9%.

The attrition rate was low. In women without epilepsy, 647 (0.6%) died pre-birth and 102 children (0.1%) died perinatally. In the epilepsy group, 8 children (1.2%) died pre-birth and 2 (0.3%) children perinatally. There were no significant differences between groups in terms of stillborns ($p = 0.1$) or perinatal deaths ($p = 0.1$).

The women reported prepregnancy weight and height. MBRN also contains prepregnancy and weight at the end of pregnancy. We calculated the body mass index (BMI) in MoBa according to $BMI = kg/m^2$. Overweight was defined as $BMI \geq 25$ and obesity as $BMI > 30$. In gestational week 30 and 6 months postpartum, the women completed the Hopkins symptom checklist, an eight-item version of a validated screening tool designed to detect depression and anxiety in population studies.¹³ Severe anxiety and depression were defined as a mean score > 2.0 in both the depression and anxiety domains.³ Information concerning pregnancy and obstetric complications such as cesarean section, excessive bleeding during delivery (>500 ml), preeclampsia (blood pressure $> 140/90$ mm Hg and proteinuria), diabetes during pregnancy, gestational hypertension (blood pressure $> 140/90$ mm Hg without proteinuria), small/large for gestational age (SGA/LGA) infants,¹⁴ head circumference, transfer of the baby to a neonatal ward, and Apgar score at 5 min after delivery was collected from the MBRN.

When studying complications during pregnancy and delivery and adverse outcome for the infant, results were stratified into the following groups: (1) overweight women with epilepsy ($n = 259$); (2) overweight women without epilepsy ($n = 30,728$); (3) normal-weight women with epilepsy ($n = 447$); (4) normal-weight women without epilepsy ($n = 67,977$); and (5) overweight women using lamotrigine ($n = 38$), carbamazepine ($n = 41$), or valproate ($n = 22$) in all combinations of drugs. Other specific AEDs were in numbers too small to allow meaningful analysis.

IBM SPSS Statistics version 21 was used. We investigated group differences using Student's *t*-test and Pearson's chi-square test (Fisher's exact test if any cross-table cell had an expected count < 5). Binary logistic regression was used to estimate the odds ratio (OR) with 95% confidence

interval (CI) for pregnancy and delivery complications adjusted for maternal age, parity, smoking, and socioeconomic factors (low household income, low education, and/or being a single mother). In this model of logistic regression, we compared groups 1 and 2, groups 1 and 3, groups 1 and 4, as well as groups 5 and 2. Additive effect was defined as epilepsy and overweight, having an independent and cumulative effect on risk estimates. We calculated this by comparing groups 1 and 2 and groups 1 and 3. If both comparisons were significant, we regarded the effect as an additive risk. Potentiating effect was defined as an increased effect compared to the expected cumulative risk of two factors. A potentiating (synergistic) effect was investigated by inserting an interaction term: multiplying epilepsy \times overweight. If the interaction terms were significant in the logistic regression model, we regarded the effect as potentiating.

MoBa has obtained a license from the Norwegian Data Inspectorate. The current study is based on version VII of the quality-assured data files released for research on epilepsy. The current study was approved by The Regional Committee for Medical Research Ethics.

RESULTS

Compared to women without epilepsy, women with epilepsy had a significantly lower age, higher weight, and BMI prepregnancy, as well as significantly more adverse socioeconomic factors (Table 1). Women with epilepsy and overweight had less weight gain during pregnancy than the nonepilepsy group without overweight.

Women with epilepsy were more often overweight and obese before pregnancy (Fig. 1). We found overweight in 38.4% of women with epilepsy and obesity in 13.2% compared to, respectively, 31.3% and 9.6% of women without epilepsy ($p = 0.001$ and $p = 0.01$). There was no significant prepregnancy weight difference between women with and without AED use during pregnancy in the epilepsy group, and there was not any significant difference between patients using AED in monotherapy and polytherapy (38.9% vs. 35.3%, $p = 0.5$). Women using carbamazepine and valproate had the highest proportion of overweight and obesity, respectively. For carbamazepine users compared to the nonepilepsy group, the significance levels were $p = 0.001$ (overweight) and $p = 0.1$ (obesity), for valproate users they were $p = 0.1$ and $p = 0.006$, respectively. There was no weight difference for women using lamotrigine compared to the nonepilepsy group ($p = 0.6$ for overweight and $p = 0.3$ for obesity).

Women with epilepsy and overweight had a high and significantly increased risk of all adverse pregnancy and delivery outcomes tested compared to normal-weight women without epilepsy, except for SGA weight and

Table 1. Maternal characteristics

	All patients		Normal BMI		Overweight			
	Epilepsy, n = 706	Nonepilepsy, n = 106,511	Epilepsy w/o overweight, n = 416	Epilepsy w/ overweight, n = 259	Nonepilepsy w/ overweight, n = 30,516	Lamotrigine w/ overweight, n = 37	Carbamazepine w/ overweight, n = 41	Valproate w/ overweight, n = 21
Age, y (mean, SD)	29.2 (4.9) ^{##}	29.8 (4.6)	28.9 (4.8)	29.9 (5.0) [#]	29.9 (4.7) ^{###}	29.1 (5.1) [*]	31.0 (4.5) ^{###}	28.8 (5.6)
Weight, kg (mean, SD)	69.5 (13.7) ^{##}	68.0 (12.9)	61.5 (6.9) ^{###}	82.3 (12.0) ^{####}	81.9 (12.2) ^{###}	81.1 (12.2) ^{###}	81.1 (13.9) ^{###}	87.0 (13.6) ^{###}
BMI (mean, SD)	24.7 (4.6) ^{###}	24.0 (4.3)	21.8 (1.9)	29.4 (3.9) ^{####}	29.1 (3.9) ^{###}	29.8 (3.9) ^{###}	28.9 (4.1) ^{###}	30.3 (3.7) ^{###}
Weight gain during pregnancy in kg (mean, SD)	15.1 (6.6)	14.9 (6.4)	15.8 (5.9)	13.8 (7.5) ^{####}	13.8 (7.5) ^{###}	14.1 (6.6)	13.8 (6.6) [#]	11.8 (6.2) ^{###}
Parity (median)	—	—	—	—	—	—	—	—
Smoking, n (%)	68 (9.7)	8,537 (8.0)	38 (9.2)	23 (8.9)	2,701 (8.7) ^{###}	3 (8.1)	2 (4.9)	2 (9.5)
Alcohol risk, n (%) ^a	41 (6.6)	6,652 (7.2)	26 (7.0)	15 (6.4)	1,675 (5.9) ^{###}	2 (5.9)	0	1 (5.3)
Adverse socioeconomic factors, n (%) ^b	116 (16.4) ^{###}	10,239 (9.5)	69 (16.6) ^{###}	40 (15.4) ^{####†}	3,234 (10.4) ^{###}	5 (13.5)	9 (22.0) ^{##}	2 (9.1)
AED ^c polytherapy, n (%)	—	—	—	—	—	13 (35.1)	9 (22)	7 (31.8)

^aAlcohol risk: Based on the T-ACE (Tolerance, Annoyance, Cut down, Eye opener) screening tool.

^bAdverse socioeconomic factors: Single mother, low educational level, low household income.

^cAntiepileptic drugs.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, compared to nonepilepsy group.

[#] $p < 0.05$, ^{##} $p < 0.01$, ^{###} $p < 0.001$, compared to normal-weight women with epilepsy.

[†] $p < 0.05$, ^{††} $p < 0.01$, ^{†††} $p < 0.001$, compared to overweight women without epilepsy.

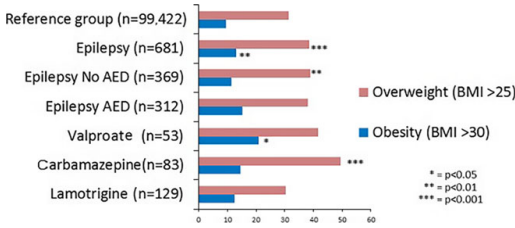


Figure 1. Percent of overweight and obesity. Epilepsia © ILAE

SGA head circumference below the 10th percentile (Fig. 2).

Unadjusted analysis showed that women with epilepsy and overweight more often had cesarean section, preeclampsia, hypertension during pregnancy, diabetes during pregnancy, small head circumference, and neonatal transfers compared to normal-weight women with epilepsy (Table 2, Fig. 2). Compared to overweight women without epilepsy, women with epilepsy and overweight more often had cesarean section, excessive bleeding during delivery, severe symptoms of depression and anxiety, SGA children, and neonatal transfer of the infant to a pediatric ward (Table 2, Fig. 2).

When we adjusted for several covariates including adverse socioeconomic factors, women with epilepsy and overweight still had significantly higher odds of cesarean section, excessive bleeding during delivery, and a twofold increased risk of severe depression and anxiety symptoms than overweight women without epilepsy (Fig. 3A). When stratifying the epilepsy group according to AED use, women using AEDs had an increased risk of cesarian section (adjusted [aOR] 1.81, 95% CI 1.2–2.7), excessive bleeding (aOR 1.56, 95% CI 1.0–2.4), SGA 2.5th percentile (aOR 3.31, 95% CI 1.3–8.2), and neonatal transfer (aOR 1.69, 95% CI 1.0–2.8) compared to overweight women

without epilepsy (Appendix S1). The epilepsy group without use of AED had an increased risk of cesarian section (aOR 1.49, 95% CI 1.0–2.2) and severe depression and anxiety (aOR 2.25, 95% CI 1.4–3.7) compared to overweight women without epilepsy (Appendix S1). Compared to women with epilepsy and normal-weight, women with epilepsy and overweight had significantly higher adjusted odds of cesarean section, preeclampsia, gestational hypertension, and neonatal transfer of the child to a pediatric unit (Fig. 3B). Of the women with epilepsy and overweight who had a cesarean section, 12.7% (n = 71) also had preeclampsia, whereas this comorbidity was shared with only 7.4% (n = 81) of normal-weight women with epilepsy with a cesarean section delivery (p = 0.28). Similarly, preeclampsia was more frequent in overweight than normal-weight women without epilepsy having a cesarean section (12.3% vs. 7.2%, p = 0.001).

Adjusted for confounders, overweight women using lamotrigine (n = 38) had a higher risk of cesarean section (OR 3.5, 95% CI 1.8–6.7, p = 0.001), severe depression and anxiety symptoms peripartum (OR 2.5, 95% CI 1.0–6.2, p = 0.04), SGA age infants (2.5th percentile) (OR 4.5, 95% CI 1.1–19.1, p = 0.04), and neonatal transfers (OR 2.8, 95% CI 1.3–6.0, p = 0.008) than overweight women without epilepsy (Fig. 4). Normal-weight women using lamotrigine, had a significant higher risk of cesarean section (OR 2.7, 95% CI 1.7–4.3, p = 0.0001) and excessive bleeding during delivery (OR 2.3, 95% CI 1.4–3.6, p = 0.0001) compared to normal-weight women without epilepsy. When comparing overweight women using valproate to overweight women without epilepsy there were no significant increase in any of the adverse outcomes tested (Appendix S1). Overweight women using carbamazepine had an increased risk of SGA 10th percentile (OR 3.5, 95% CI 1.5–8.3, p = 0.005) compared to overweight women without epilepsy (Appendix S1).

The reasons for neonatal transfer to a pediatric ward were similar for all groups examined (Appendix S1).

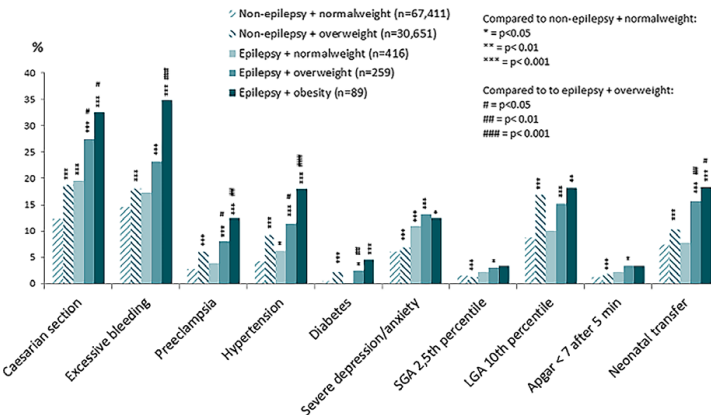


Figure 2. Unadjusted proportions of complications during pregnancy and delivery. Epilepsia © ILAE

Table 2. Complications during pregnancy, delivery, and for birth outcome

	Normal BMI (%)		Overweight (%)				
	Epilepsy w/o overweight, n = 416	Nonepilepsy w/o overweight, n = 67,411	Epilepsy w/ overweight, n = 259	Nonepilepsy w/ overweight, n = 30,516	Lamotrigine w/ overweight, n = 37	Carbamazepine w/ overweight, n = 41	Valproate w/ overweight, n = 21
Cesarean section	81 (19.5)	8,420 (12.4)	71 (27.4) ^{***#†††}	5,769 (18.8)	16 (42.1) ^{***}	10 (24.4)	6 (27.3)
Excessive bleeding	72 (17.3)	9,849 (14.6)	60 (23.2) ^{*†}	5,542 (18.1)	9 (23.7)	9 (22.0)	6 (27.3)
Preeclampsia	16 (3.8)	1,829 (2.7)	21 (8.1) ^{††}	1,858 (6.1)	3 (7.9)	4 (9.8)	3 (13.6)
Hypertension during pregnancy	26 (6.3)	2,905 (4.3)	29 (11.4) ^{††}	2,835 (9.3)	6 (15.8)	6 (15.0)	3 (13.6)
Diabetes	1 (0.2)	350 (0.5)	6 (2.4)	636 (2.1)	3 (8.1) [*]	0	0
Severe depression/anxiety	45 (10.9)	4,067 (6.1)	34 (13.2) ^{***#†††}	2,095 (6.9)	6 (15.8) [*]	4 (9.8)	1 (4.5)
SGA 10th percentile	42 (10.1)	5,147 (7.6)	20 (7.7)	1,623 (5.3)	3 (7.9)	6 (14.6) ^{**}	1 (4.5)
SGA 2.5th percentile	9 (2.2)	1,091 (1.6)	8 (3.1) ^{*††}	378 (1.2)	2 (5.3) [*]	2 (4.9) [*]	0
LGA 10th percentile	41 (10.0)	5,940 (8.9)	38 (15.1)	5,107 (16.9)	6 (16.2)	2 (5.0) [*]	3 (13.6)
SGA head circ 10th perc	43 (10.5)	5,737 (8.6)	15 (6.0) ^{††}	1,722 (5.7)	1 (2.7)	5 (12.5)	0
Apgar < 7 after 5 min	9 (2.2)	885 (1.3)	8 (3.3)	558 (1.9)	1 (2.7)	0	1 (4.8)
Neonatal transfer	31 (7.8)	4,726 (7.4)	37 (15.6) ^{***#†††}	2,996 (10.4)	9 (23.7) ^{**}	5 (13.9)	4 (19.0)

Cesarean delivery: either elective or urgent operational delivery; excessive bleeding: >500 ml during delivery; preeclampsia: blood pressure > 140/90 mm Hg and proteinuria; diabetes during pregnancy: gestational diabetes and diabetes type 2; hypertension during pregnancy: blood pressure > 140/90 mm Hg without proteinuria; SGA 10th/2.5 percentile or LGA 10th percentile: small/large for gestational age (SGA) babies; SGA head circ 10th perc: small head circumference for gestational age, 10th percentile; neonatal transfer: transfer to neonatal ward after birth; Apgar score < 7 after 5 min: low score of appearance, pulse, grimace, activity, and Respiration.

Unadjusted comparisons.

*p < 0.05, **p < 0.01, ***p < 0.001, compared to nonepilepsy with overweight.

#p < 0.05, ##p < 0.01, ###p < 0.001, compared to epilepsy without overweight.

†p < 0.05, ††p < 0.01, †††p < 0.001, compared to overweight women without epilepsy.

DISCUSSION

Epilepsy is known to cause complications during pregnancy. However, there have been no previous studies where mechanisms behind the increased risk have been targeted. To improve the pregnancy outcome in women with epilepsy, risk stratification is needed. Our study shows that overweight contributes significantly to the increased complication risk during pregnancy and after delivery in women with epilepsy. Both compared to overweight women without epilepsy and normal-weight women with epilepsy, overweight women with epilepsy are at an especially increased risk for several complications during pregnancy and in the perinatal period. This shows that a significant proportion of pregnancy-related complications that women with epilepsy experience is applicable to overweight. This new information is important, as overweight is a modifiable risk factor.

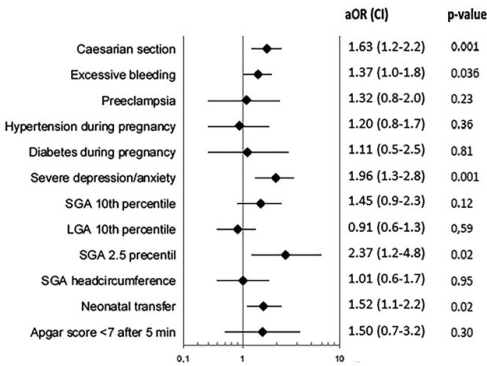
We also found that women with epilepsy were more often overweight than women without epilepsy.

Epilepsy and overweight had an additive effect on outcome for some of the parameters, including cesarean section, excessive bleeding during delivery and transfer to a neonatal ward. The three most common indications for cesarean section are failure to progress during labor, abnormal fetal status, and fetal malrepresentation.¹⁵ Epilepsy is an indication for cesarean delivery if a seizure occurs during the second stage of labor, or the patient is unable to cooperate due to sedation.¹⁶ Most chronic diseases increase cesarean delivery rates.¹⁷ Elective cesarean section is the most

frequent mode of delivery for women with preeclampsia.¹⁸ In women with epilepsy who had a cesarean section, preeclampsia rates were numerically higher in the overweight group compared to the normal-weight group, as also seen in women without epilepsy. Preeclampsia was therefore a reason for operational delivery in both women with and without epilepsy, but cannot fully explain the additive effect overweight had on risk of cesarean section in the epilepsy group.

Maternal overweight and obesity in otherwise healthy women are associated with several adverse outcomes such as gestational diabetes,¹⁹ gestational hypertension,¹⁹ preeclampsia,¹⁹ cesarean delivery,²⁰ low Apgar score,²¹ preterm birth,²² stillbirth,²³ neonatal death,²⁴ and large for gestational age (LGA) infant.²⁵ The risk increases with increasing degrees of overweight/obesity.²⁶ It is not fully understood whether overweight is a cause of adverse pregnancy outcome or whether the association between overweight and complications during pregnancy is due to shared characteristics of both entities, such as adverse socioeconomic factors or poor health. However, we adjusted for socioeconomic factors (low household income, low education, and/or being a single mother) in our analyses, as well as for smoking, parity, and maternal age. Complications during pregnancy in overweight women are often attributed to the increase in gestational diabetes, but overweight women who are glucose tolerant are still at a greater risk of adverse pregnancy outcome.²⁷ Therefore, other mechanisms play a part.

A Epilepsy with overweight (n=259) vs non-epilepsy with overweight (n=30,728), adjusted for AED, parity, age, smoking and socioeconomic factors



B Epilepsy with overweight (n=259) vs epilepsy without overweight (n=447), adjusted for parity, age, smoking and socioeconomic factors

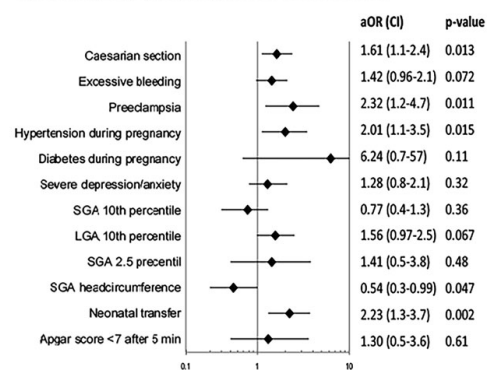


Figure 3. (A, B) Risk of complications during pregnancy and delivery. Epilepsia © ILAE

Lamotrigine users with overweight (n=38) vs non-epilepsy with overweight (n=30,516), adjusted for parity, age, smoking and socioeconomic factors.

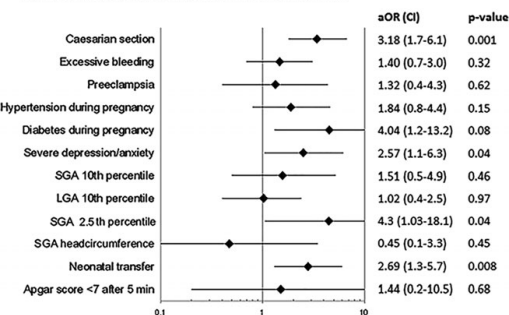


Figure 4. Risk of complications during pregnancy and delivery for overweight women using lamotrigine. Epilepsia © ILAE

In our study, overweight contributed more than a diagnosis of epilepsy to the increased risk of gestational diabetes, gestational hypertension, preeclampsia, and delivery of a LGA infant. This effect was not mediated by AED use, as we also investigated the epilepsy group by stratifying into groups with and without use of AEDs. AEDs did have an effect on the risk of excessive bleeding, having SGA children and transfer of the infant to a neonatal ward. However, having epilepsy was the main generator of anxiety and depressive symptoms, as the risk was increased in women both using and not using AEDs compared to the other women. Peripartum depression is frequent in women with epilepsy,²⁸ but seldom medically treated.²⁹ According to prior investigations of the MoBa epilepsy cohort, peripartum anxiety and depression were strongly associated with frequent epileptic seizures during pregnancy, prepregnancy depression and anxiety, a history of physical or sexual abuse, having lost a child, as well as unplanned pregnancy. These associations are probably more related to the epilepsy disorder itself rather than any comorbid overweight. In addition, the increased frequency of neonatal transfers to a children's ward depended more on having epilepsy than on being overweight, indicating a greater need for closer observation and/or treatment of the newborn in maternal epilepsy regardless of maternal weight.

Because overweight influenced the frequency of pregnancy and delivery complications, obese women with epilepsy should be regarded as a high-risk group and receive extra care in the pregnancy and perinatal period. Blood sugar levels, blood pressure, and signs of preeclampsia should be monitored carefully. Additional ultrasound investigations should be considered in order to detect potential fetal growth anomalies or malformations. Screening for maternal symptoms of anxiety and depression is also warranted. Anxiety and depression may cause severe adverse consequences for the mother and child, and therefore swift treatment is important.²⁹ Antenatal vitamin K supplements are often given routinely to women using an enzyme-inducing AED, such as carbamazepine or phenytoin to avoid bleeding.³⁰ Because the risk of bleeding was increased in overweight women using AEDs compared to other overweight women, but not compared to normal weight women with epilepsy, AEDs may be the causative factor. AEDs may also cause bleeding by uterine atony.³⁰

Most previous studies on pregnancy and delivery complications in epilepsy have not adjusted for overweight and obesity.² Such adjustment should be a prerequisite, as we show that women with epilepsy are more overweight than control women also in relation to pregnancy. The association between weight and AED use was modest, suggesting that the increased weight also was moderated by other factors. Weight tends to increase with number of pregnancies, but there was no difference in parity in women with epilepsy

compared to the nonepilepsy group. Our results are in line with other reports on weight in epilepsy populations.^{31–33} In a study of people with epilepsy recruited from an adult epilepsy clinic; BMI, waist circumference, and information regarding physical activity were obtained.³¹ There was an association between obesity, idiopathic generalized epilepsy, and family history of epilepsy. The epilepsy group participated less in physical activities and had a higher BMI, supporting that greater weight in epilepsy is affected by lifestyle.³² People with epilepsy have previously been discouraged from participation in physical activity because of fear of inducing seizures.³⁴ The recommendation may have caused people with epilepsy to exercise less, thereby increasing obesity rates. Exercise was a seizure precipitant in 10% of patients with epilepsy.³⁴ However, in the majority of patients, physical exercise has no adverse effects. One third of patients claimed that exercise even contributes to improved seizure control.³⁴ Physical activity during pregnancy will also have positive effects on birth outcome. For women with a BMI < 30, the lowest perinatal mortality was seen in those performing recreational physical activity at least once a week.⁵ Exercise should be encouraged also in women with epilepsy, and especially during their childbearing years.

In our material, valproate and carbamazepine were particularly associated with overweight and obesity. AEDs influence body weight, and some cause overweight.⁷ A possible explanation is the effect on hormonal balance. Liver enzyme-inducing AEDs, as well as valproate, alter levels of sex hormones and thyroid function,³⁵ which in turn may affect weight gain. Low serum leptin level is associated with weight loss in overweight female patients with epilepsy.³⁶ Zonisamide reduces serum leptin levels, and this may explain the association of zonisamide with weight loss.³⁶ Other AEDs could also influence leptin and associated hormones. There are also indications that epilepsy itself has an effect on hormonal balance, especially sex hormones,³⁷ which in turn is associated with polycystic ovary syndrome. This syndrome alters distribution of adipose tissue and causes overweight. Adipose tissue itself is also an active endocrine organ that could enhance the effects of AEDs on hormonal balance.

We found that women using lamotrigine were especially at risk for complications such as cesarean section and severe peripartum depression and anxiety if they were overweight. Giving birth to a very small infant and neonatal transfer of the child was frequent. The adverse effects on the child did not seem to apply for women using lamotrigine if they were normal weight. The increased complication rates were not seen for overweight women using carbamazepine or valproate (Appendix S1). Lamotrigine is considered to be a relatively safe drug during pregnancy,³⁸ although it has been linked to a greater risk of preeclampsia and bleeding.¹ Lamotrigine is associated with reduced seizure control during pregnancy, possibly due to increased hepatic drug

elimination during pregnancy.³⁹ This may in part explain the high complications rates for lamotrigine in our study. There is also the possibility of selection bias, in that clinicians may have subscribed lamotrigine to patients who were vulnerable in terms of mental health issues such as depression and anxiety. This is backed up by the increased risk that overweight women using lamotrigine have of depression and anxiety peripartum compared to overweight women without epilepsy (OR 2.29, CI 1.4–3.7). The results for other AED groups may be influenced by a lower statistical power, as there were numerical increased risks for several variables (Appendix S1). There is a possibility that polytherapy may have an effect, but rates of polytherapy were similar in all AED groups studied.

Strengths of the present study include a large study population and a prospective design. The participation rate of 41% at first assessment is as expected for population-based studies.⁴⁰ Because filling out the questionnaires requires some effort, it is possible that the MoBa participants were more resourceful than nonparticipants. However, this is not expected to influence or bias effect measures.⁹ A strength of the present study is the inclusion also of women with resolved/inactive epilepsy who were not using AEDs during pregnancy. A retrospective study of the MoBa cohort showed that the frequency of seizures during pregnancy in women not taking AEDs was 10.7% the last 2 years and 16.8% the last 5 years before pregnancy.¹¹ A self-reported diagnosis of epilepsy might be less accurate than a diagnosis reported by medical professionals. However, the epilepsy diagnosis and medication were validated by linkage to the MBRN, hospital records (diagnosis not confirmed for 5%), blood samples (detection rate 95%), and with a retrospective questionnaire (PPV 98.8%, specificity 99.9%).^{10,11} There was no significant difference in the prevalence estimates of epilepsy in the MoBa cohort and the total population.⁹ Complications during pregnancy, delivery, and birth outcome were reported by midwives and physicians. Given that the MoBa study contains >100,000 participants, the statistical power in our study was high. Nevertheless, some AED subgroups were underpowered, and we were not able to do monotherapy analyses. However, the proportion of polytherapy users was similar in all AED groups.

CONCLUSION

Our results show that the combination of overweight and epilepsy exposes mother and child to a significantly increased risk of complications during pregnancy and in the perinatal period. Overweight is a preventable risk factor. Referral to a nutritionist should be considered for young women with epilepsy when an AED is initiated and when pregnancy is planned. Exercise should be encouraged to reduce weight. Overweight and obese women with epilepsy should be regarded as a high-risk group during pregnancy and be followed closely. In particular, symptoms indicating

pre-eclampsia, hypertension, intrauterine growth restriction, as well as perinatal depression and anxiety should be monitored. Heredity, physical activity, lifestyle, antiepileptic medication, and diet are all probable mediators for overweight and obesity in epilepsy.

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DISCLOSURE OF CONFLICT OF INTEREST

Nils Erik Gilhus has received speaker's honorarium from Merck-Serono, Baxter, and Octapharma. Marte Helene Bjørk and Gyri Veiby have received lecture honoraria from GlaxoSmithKline and congress travel support from UCB Pharma. Eivind Kolstad has no conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Detailed results of regression analysis.

Young people with epilepsy have an increased risk of eating disorder and poor quality diet

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SUMMARY

Objective: To investigate whether adolescents with epilepsy are at increased risk of having self-reported eating disorder symptoms and poor quality diet compared to young people from the general population.

Methods: We used data from the Health Profile for Children and Youth in Akershus Study, a cross-sectional population-based study based on a voluntary self-reported questionnaire. There were 19,995 participants (response rate 85%) aged 13–19 years; 247 (1.2%) reported a lifetime diagnosis of epilepsy. Odds ratios (OR) and 95% confidence intervals (CI) for eating disorders, unhealthy diet, dieting, satisfaction with looks, and participation in sports were estimated by using a logistic regression model. All estimates were adjusted for single parents and poor family economy.

Results: Children and adolescents with epilepsy had more eating disorders than their peers (OR 1.8, CI 1.0–3.0, $p = 0.03$). They were less satisfied with their own appearance (OR 0.7, CI 0.5–0.9, $p = 0.02$), and they eat more unhealthily (OR 1.7, CI 1.3–2.2, $p = 0.001$). Males with epilepsy were more likely to have been dieting (OR 3.1, CI 1.2–7.9, $p = 0.02$) and less satisfied with their own appearance (OR 0.4, CI 0.3–0.7, $p < 0.001$). Females with epilepsy were more likely to eat unhealthily (OR 1.7, CI 1.1–2.5, $p = 0.01$).

Significance: Adolescents with epilepsy are at increased risk of having eating disorder symptoms. They eat less healthily and are less satisfied with their looks. Health workers should be aware of this and bring diet and lifestyle into the dialogue with young people with epilepsy.

KEY WORDS: Epileptic, Psychiatric, Adolescents, Overweight, Children.



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Epilepsy is a common neurological disorder with a prevalence of 0.6–1.2%.^{1–3} Epilepsy in adolescents is associated with comorbid disorders such as depression, anxiety, attention-deficit/hyperactivity disorder (ADHD), and low self-

esteem.^{4–7} Boys with epilepsy are prone to risk-taking behavior.⁸ The relation between epilepsy and eating disorders has been scarcely studied, and not at all in adolescents. A population-based study from England found an increase in risk of eating disorders among people with epilepsy in general.³ Pregnant women with epilepsy in Norway also more frequently reported an eating disorder than other women, especially binge eating disorder.^{9,10} The prevalence of eating disorders among adolescents continues to increase¹¹ and is a predictor of negative outcome in terms of mental health disorders, substance abuse, deliberate self-harm, and overweight or underweight.^{12,13} Thus, there is a demand for further knowledge within this field. Our aim was to investigate whether adolescents with epilepsy more often than their peers had eating disorder symptoms and eating-associated problems such as frequent dieting and

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KEY POINTS

- Adolescents with epilepsy are at an elevated risk of suffering from eating disorder symptoms
- They eat less healthily and are less satisfied with their looks
- Referral to a nutritionist should be considered in young people with epilepsy at the time of diagnosis

negative feelings toward their own appearance. We also wanted to study quality of diet in adolescents with epilepsy.

METHODS

We used data from the Health Profile for Children and Youth in Akershus Study.¹⁴ This cross-sectional population-based study was based on a voluntary self-reported questionnaire. The relevant questions for this investigation are listed in the Appendix. The study was conducted by the Norwegian Health Services Research Centre in 2002. Random school classes from all municipalities in Akershus County were selected, and all pupils aged 13–19 years in the selected classes were invited to participate. Their parents were informed and gave consent. A total of 19,995 adolescents answered, yielding an 85% response rate; 0.4% of pupils in Norway attended special schools in 2002 and were excluded from this study.¹⁵ Special schools are for children and adolescents with disabilities such as mental retardation. The questionnaire comprised 110 questions grouped under the main topics: sociodemographic conditions, social network and school, smoking, alcohol, drug abuse, nutrition and attitude concerning body, physical health, psychosocial health, mental health, use of health services.¹⁶ The questionnaires were completed during a classroom session and were all anonymous.

The epilepsy diagnosis was self-reported. The participants answered the simple question of whether they had or had had epilepsy. This question could be answered by “yes,” “no,” or “don’t know.” The answer “yes” counted as having epilepsy, and “no” and “don’t know” counted as not having epilepsy. Two hundred forty-seven individuals (1.2%) reported a diagnosis of epilepsy. In an exploratory analysis those who answered “don’t know” were excluded. All other participants constructed the reference group. Questions concerning asthma were asked in the same way as for epilepsy. All individuals reporting this diagnosis formed a control group of chronic disease ($n = 3,320$). This group was also a part of the total reference group ($n = 19,748$).

Outcome variables

For the purposes of this investigation, reporting having sought help from health personnel for an eating disorder was used as a proxy for a diagnosis of an eating disorder. Participants reported whether they had visited a school

nurse or other health personnel with an eating disorder as the main issue. Participants’ diet was investigated. An unhealthy diet was defined prestudy by nutritionists as eating or drinking candy, potato chips, french fries, or sugar-containing soda daily. The participants reported whether they were or previously had been on a diet to reduce weight. They also noted whether they were satisfied with their own body appearance (yes/no) and whether they wanted to improve their looks (yes/no). Finally, the level of physical exercise was recorded. Participants reported how often they were physically active, and the alternatives were (1) never, (2) less than once a month, (3) once a month, (4) once a week, (5) 2–3 times a week, (6) 4–6 times a week, and (7) every day. A dichotomous variable was constructed where the cut-off was set at being physically active two or more times a week. Mean age of menarche was calculated for female participants.

Covariates

Perceived low family income, living with a single parent, and depressive symptoms were used as covariates. Depressive symptoms were assessed using SDQ-S (Strength and Difficulty Questionnaire), a tool frequently used to screen for psychiatric symptoms with good psychometric properties.^{16,17} These data has been reported for this population previously.⁸ The appropriate questions are listed in the Appendix.

Statistics

For statistical analysis we used SPSS version 22. Chi-square tests (Fisher exact test for an expected cell count <5) and t test were used to investigate group differences, and odds ratios with 95% confidence intervals were obtained using logistic regression. The logistic regression models were adjusted for reported low family income and living with a single parent. Both logistic univariate and multivariable analyses were performed to investigate associations between variables. Eating disorder was set as the dependent factor and dieting, unhealthy diet, satisfaction with own body appearance, desire to change looks, depressive symptoms, and age, sex, overweight, family economy, single parent, and smoking as independent factors within the epilepsy group. The independent factors were first tested separately in univariate analyses. Criterion for variables to enter the multivariate analysis was set at $p < 0.1$. Satisfaction with own body appearance and desire to change looks were not included in the same multivariate analysis owing to collinearity with dieting.

The study was approved by the regional ethics committee (REK, ref. 40-02022).

RESULTS

Background information is provided in Table 1. Mean age and mean height were similar in the epilepsy and reference populations as well as for the group with other chronic

Table 1. Background data

	Epilepsy n = 247	Reference n = 19,995	Males with epilepsy n = 137	Male controls n = 10,180	Females with epilepsy n = 108	Female controls n = 9,703	Asthma n = 3,320
Age (SD)	16.1 (1.4)	16.2 (1.5)	16.1 (1.4)	16.2 (1.5)	16.1 (1.4)	16.2 (1.5)	16.2 (1.5)
Height in cm (SD)	174.7 (9.4)	173.8 (9.0)	180.5 (7.5)	179.8 (7.1)	167.5 (6.5)	167.4 (6.0)	173.3 (9.2)
Weight in kg (SD)	67.5 (11.8)*	65.4 (11.7)	72.8 (11.4)	71.3 (11.1)	60.9 (9.0)	59.1 (8.8)	66.2 (12.1)**
Smoking (%)	78 (32.9%)**	4,180 (24.2%)	45 (34.4%***)	1,877 (21.4%)	33 (31.4%)	2,278 (27.0%)	913 (28.0%***)
Overweight BMI >25 n (%)	13 (13.0%)	1,047 (12.6%)	8 (13.8%)	677 (15.7%)	5 (11.9%)	364 (9.2%)	246 (15.9%***)
Obesity BMI >30 n (%)	2 (2.0%)	172 (2.1%)	1 (1.7%)	102 (2.4%)	1 (2.4%)	69 (1.7%)	45 (2.9%)*

BMI, body mass index; SD, standard deviation.
*p < 0.05, **p < 0.01, ***p < 0.001 compared to the reference group.

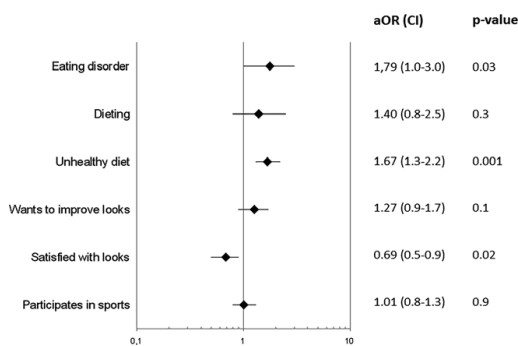


Figure 1. Eating-related factors in the epilepsy group (n = 247) vs. the reference group (n = 19748).
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diseases. The epilepsy group and the group with other chronic disease were significantly heavier than the reference group and more often reported nicotine smoking.

People with epilepsy between 13 and 19 years more often reported having an eating disorder (OR 1.79, CI 1.0–3.0, $p = 0.03$) and an unhealthy diet (OR 1.67, 1.3–2.2, $p = 0.001$) than the reference group. Young people with epilepsy had a significant higher daily consumption of candy, sugar-containing soda, potato chips, and pommies frites than adolescents without epilepsy (Fig. 1). They were also significantly less satisfied with their own body appearance (OR 0.69, CI 0.5–0.9, $p = 0.02$) (Table 2; Fig. 2). Results did not change when people who did not know whether they had epilepsy or not were excluded from the analysis.

Females with epilepsy were more prone to an unhealthy diet (OR 2.16, CI 1.5–3.2, $p = 0.001$) compared to females in the reference group (Fig. 3). Males with epilepsy were more likely to be dieting (OR 3.12, 1.2–7.9, $p < 0.02$) than their peers and reported being less satisfied with their body appearance (OR 0.44, 0.3–0.7, $p < 0.001$) (Fig. 4). These differences were not as prominent in females with epilepsy

(Fig. 3). A group of adolescents with the chronic disease asthma scored in between the epilepsy group and the reference group for all variables (Table 2).

There was no difference in age of menarche in the epilepsy group (mean age 12.6, SD 1.4) and the reference group (mean age 12.6, SD 1.2).

In the univariate logistic regression analysis within the epilepsy group there was a significant inverse association between eating disorder and satisfaction with looks (OR 0.2, CI 0.06–0.58, $p = 0.004$), between an eating disorder and a desire to change looks (OR 5.1, CI 1.8–15.1, $p = 0.003$), and between seeking help for eating disorders and dieting (OR 89.3, CI 4.5–542.0, $p < 0.001$), although CI for the latter analysis was wide. There was no significant association between eating disorder and depressive symptoms, with family economy, living with a single parent, or with being overweight (OR 1.44, CI 0.5–4.5, $p = 0.53$). However, there was an association between satisfaction with looks and family economy (OR 3.58, CI 1.5–8.7, $p = 0.005$). There was an inverse association in the epilepsy group between satisfaction with looks and dieting (OR 0.05, CI 0.01–0.2, $p < 0.001$). Only dieting remained significantly associated with having an eating disorder in the multivariate model (OR 47.9, CI 4.5–511.9, $p = 0.01$).

DISCUSSION

Key findings

Our main finding is an increased rate of eating disorder symptoms in an unselected and population-based cohort of adolescents with epilepsy compared with a reference group. This is an important finding in a group that is known to be at risk of several psychiatric disorders.^{5,9,16,18} Better knowledge should increase awareness and lead to a better holistic treatment of epilepsy. Apart from their immediate impact, eating disorders can result in physical problems later in life, such as impaired bone density, reduced skeletal function,¹⁹ and impaired reproductive health in women.²⁰ Perhaps more importantly, however, eating disorders also represent a predictor of mental health disorders, substance abuse, and deliberate self-harm.^{12,13} The presence of an eating disorder

Table 2. Eating-related outcome

	Epilepsy (n = 245)	Reference (n = 19,995)	Males with epilepsy (n = 137)	Reference males (n = 10,180)	Epilepsy female (n = 108)	Reference female (n = 9,703)	Asthma (n = 3,320)
Eating disorder n (%)	8 (5.4%)**	210 (2.0%)	3 (4.3%)*	50 (1.1%)	5 (6.7%)*	159 (2.8%)	54 (2.7%)*
Dieting n (%)	13 (5.3%)	655 (3.7%)	5 (3.6%)**	94 (1.1%)	8 (7.4%)	559 (6.5%)	148 (4.5%)*
Unhealthy diet n (%)	119 (51.7%***)	6,718 (39.0%)	65 (52.8%)	3,919 (45.0%)	54 (54.9%***)	2,762 (32.7%)	1,481 (48.0%***)
Wants to improve looks n (%)	60 (24.3%)	3,490 (19.8%)	21 (15.3%)*	903 (10.1%)	39 (36.1%)	2,577 (30.1%)	657 (19.8%)
Satisfied with looks n (%)	174 (77.0%)*	14,258 (83.2%)	104 (83.9%***)	8,004 (92.6%)	70 (68.6%)	6,187 (73.5%)	2,589 (80.6%***)
Participates in sports n (%)	158 (66.7%)	11,636 (66.9%)	82 (63.6%)	6,292 (71.4%)	75 (70.1%)	5,285 (62.1%)	2,220 (67.8%)

*p < 0.05, **p < 0.01, ***p < 0.001 compared to the reference group.

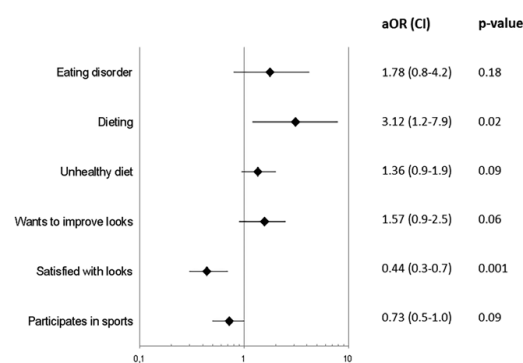


Figure 2.

Eating-related factors in males with epilepsy (n = 137) vs. males in the reference group (n = 10180).

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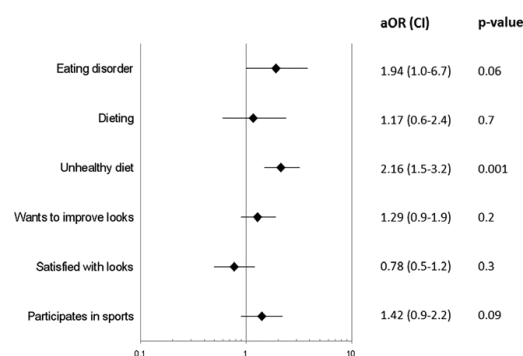


Figure 3.

Eating-related factors in females with epilepsy (n = 108) vs. females in the reference group (n = 9703).

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before pregnancy has been associated with a greater likelihood of pregnancy complications in patients with epilepsy.⁹ This is also seen among the general population, where

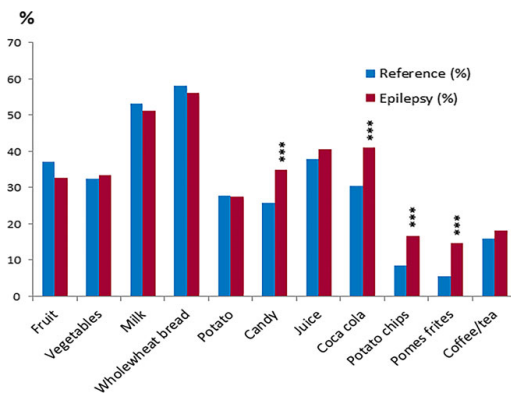


Figure 4.

Frequency (percent) of young people with a daily consumption of various food categories in the epilepsy (n = 247) vs. the reference group (n = 19748). ***p < 0.001 compared to the reference group.

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maternal eating disorders have been associated with impaired fetal growth and impaired growth in the children during their first year.²¹ Furthermore, children of mothers with eating disorders have been shown to be at increased risk of psychiatric disease in childhood.²² This highlights the importance of early detection and intervention regarding eating disorders, both in the general population, but especially among patients with epilepsy who may also have additional problems.

The etiology of eating disorders is largely unknown. Both genetic predisposition and environmental and sociocultural influences are thought to be relevant etiologic factors for eating disorders,²³ but none of these should be specific for epilepsy. However, some antiepileptic drugs (AEDs) contribute to a weight increase,²⁴ and eating disorders may arise as a response to these changes. Another contributing factor may be that failure to control seizures may prompt a need in patients with epilepsy to gain control over their body in a

different way. By focusing attention on weight, shape, and eating, epilepsy patients may feel that they are in a domain where control is possible.²⁵ Furthermore, people with epilepsy have a higher burden of psychiatric comorbidity, such as anxiety and depression,²⁶ and eating disorders could be associated with these conditions. Anxiety and depression are frequent comorbid conditions in people with eating disorders.¹³ However, in our material there was no association between an eating disorder and depressive symptoms within the epilepsy group.

In our study, adolescents with epilepsy appeared to have a diet of poorer quality than their peers without epilepsy. An unhealthy diet is a growing concern and a major cause of morbidity and disability worldwide,²⁷ partly because it leads to overweight and obesity. These conditions are mainly concerns of developed countries and could also be seen as a socioeconomic problem.²⁸ However, despite the less healthy diet in the young people with epilepsy, we did not find an increased rate of overweight, although they were heavier. Increased frequency of overweight in patients with epilepsy has been reported in other cohorts.²⁹

The chronic disease asthma scored in between the epilepsy group and the reference group in terms of risk of eating disorder, dieting, unhealthy diet, and dissatisfaction with own appearance. This emphasizes that young people with epilepsy are especially vulnerable in terms of developing bad eating habits and eating disorders.

A risk of eating disorders and poor diet quality should be evaluated in young people with epilepsy, and referral to a nutritionist at the time of diagnosis as well as when starting on AEDs should be considered. Exercise and a healthy lifestyle should be encouraged in all adolescents but particularly among those with epilepsy. In some cases exercise will help control seizure frequency.³⁰

Dissatisfaction with own body appearance was more frequent in adolescents with epilepsy than in the reference group. This may reflect the stigma that many epilepsy patients feel influences their lives,³¹ which affects their quality of life and leads to anxiety and depression. An increased rate of hyperactivity/inattention problems, anxiety, and depression has previously been reported also in our epilepsy cohort.⁵ Dissatisfaction with own appearance was associated with dieting and a wish to improve looks. There was also an association between poor family economy and a dissatisfaction with own body appearance.

Strengths and limitations

A large sample size and very high response rate (85%) are the main strengths of this study. A major strength is also the population-based nature of the study. Because a large proportion of the invited youths participated, we avoided the overestimation of adverse outcomes that often occurs in clinical materials. Randomization of selected school classes was performed, and, because of the organization of the Norwegian school system with

almost all children (>96% in 2015) attending ordinary state-funded schools, an accurate representation of the population was obtained. Our reference group consisted of youths who were representative of the general population and not only healthy individuals; hence we avoided inflation of the rates of adverse outcomes in the epilepsy group. We were also able to compare the epilepsy group with a relevant control group with a nonneurological chronic disease and to assess the relationship between epilepsy, eating disorders, diet, and socioeconomic status. The main limitation of this study is the lack of clinical information, such as type of eating disorder, type of epilepsy, seizure frequency, and treatment. In addition, we were not able to classify the types of eating disorder. Adolescents with severe disabilities, including severe mental retardation, were excluded from this study if they were not attending general public schools (0.4% of pupils in Norway in 2002).¹⁵ This means that we have possibly excluded people with the most disabling epilepsy but also we have excluded those with similar disabilities who are not epileptic. It might be assumed that our findings would be even more pronounced if only people with active epilepsy and using AEDs had been included.

Significance

Both female and male adolescents with epilepsy are at an elevated risk of suffering from eating disorder symptoms. They eat less healthily than their peers without epilepsy and are less satisfied with their own appearance. Health workers should be aware of these associations between epilepsy, eating disorders, and diet and introduce diet and lifestyle into their dialogues with young people with epilepsy. Referral to a nutritionist should be considered in young people with epilepsy at the time of diagnosis as well as when initiating antiepileptic medication.

CONFLICT OF INTEREST

N.E.G. has received speaker's honoraria from Merck-Serono, Baxter, and Octapharma. M.H.B. has received lecture honoraria from GlaxoSmith-Kline and congress travel support from UCB pharma. M.L. has received lecture honoraria from Eisai and UCB pharma. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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APPENDIX ITEMS FROM QUESTIONNAIRE USED IN THE PAPER:

- 1 Are you male or female?
- 2 In what year were you born?
- 3 Do you live with your mother, father, or both?
- 4 How much do you weigh?
- 5 How tall are you?
- 6 Do you have or have you had asthma, diabetes, or epilepsy? (yes/no)
- 7 Do you smoke? (yes/no)
- 8 How often do you smoke? (1. Not at all. 2. Less than once a week. 3. Every week. 4. Every day.)
- 9 How often do you participate in sports? (1. Not at all. 2. Less than once a month. 3. Once a month. 4. Once a week. 5. 2–3 times a week. 6. Every day.)
- 10 How often do you eat/drink fruit, vegetables, whole-wheat bread, dairy products, potatoes, candy, juice, sugar-containing soda, potato chips, hamburger, and sausages? (1. seldom/never. 2. Less than once a week. 3. Once a week. 4. Several times a week. 5. Every day. 6. Several times a day.)
- 11 Have you ever tried dieting to lose weight? (yes/no)
- 12 Are you satisfied with your appearance? (yes/no)
- 13 Do you want to change your appearance? (yes/no)
- 14 How old were you when you first had your period?
- 15 Have you ever sought help of health personnel because of an eating disorder? (yes/no)

From Fig. 1: Analyses where the epilepsy group is compared to a reference group that denied having epilepsy. Those who answered “don’t know” are excluded.

	OR (CI)	p-value
Eating disorder	1.82 (1.1–3.1)	0.02
Dieting	1.48 (0.8–2.6)	0.2
Unhealthy diet	1.47 (1.1–1.9)	0.005
Wants to improve looks	1.08 (0.8–1.4)	0.5
Satisfied with looks	0.67 (0.5–0.9)	0.01
Participates in sports	1.2 (0.8–1.7)	0.2



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