Drivers for the Comorbidity of Type 2 Diabetes Mellitus and Epilepsy: a Scoping Review

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Abstract:
Epilepsy, a common neurologic condition, is associated with a greater prevalence of type 2 diabetes mellitus (T2DM). We examined potential drivers for the comorbidity of epilepsy and T2DM in an attempt to elucidate possible biological mechanisms underlying the development of processes in individuals. We searched PubMed and Medline up to December 2019. Our search yielded 3,361 articles, of which 82 were included in the scoping review. We reviewed articles with a focus on the association of epilepsy and T2DM, drivers, and biological mechanisms. Epilepsy is associated with obesity and obesity is associated with T2DM. Treatment with valproate (either sodium or acid) is associated with weight increase and hyperinsulinemia, while topiramate causes weight loss. People with epilepsy are less likely to exercise which is protective against obesity. Mitochondrial dysfunction and adiponectin deficiency are common to epilepsy and T2DM. One possible mechanism for the comorbidity is mitochondrial dysfunction and adiponectin deficiency which promotes epilepsy, obesity, and T2DM. Another possible mechanism is that people with epilepsy are more likely to be obese due to lack of exercise and the effects of some antiseizure medications, which makes them susceptible to T2DM due to the development of mitochondrial dysfunction and adiponectin deficiency. A third mechanism is that people with epilepsy have greater mitochondrial dysfunction and lower adiponectin levels than people without epilepsy at baseline, which may exacerbate after treatment with antiseizure medications. Future research involving a combined genetic and molecular pathway approach will likely yield valuable insight regarding the comorbidity of epilepsy and T2DM.

1. Introduction

Epilepsy, a common neurologic symptom-complex contributing to disability and premature mortality, is associated with a greater prevalence of comorbidities [1, 2]. A European cohort study found the cumulative probability of comorbid illness was significantly greater for people with epilepsy than healthy controls and higher seizure frequency associated with a greater number of comorbid conditions [3]. A Norwegian cohort study found that over three-quarters of children with epilepsy had one or more comorbid disorders, compared to only about a third of children in the general population [4]. People with drug-refractory epilepsy have higher comorbidity rates than people with controlled epilepsy [5].

A disorder of particular interest is diabetes [6-9]. The connection between epilepsy and type 1 diabetes mellitus (T1DM) has already been highlighted [10-20]. A recent meta-analysis found that people with T1DM have a 2 to 6 fold increased risk of epilepsy than the general population [20]. The onset of T1DM precedes the onset of epilepsy by a mean period of 1.5-2.8 years [20].

Data regarding the comorbid association of epilepsy and type 2 diabetes mellitus (T2DM) are sparser but exist. A cohort study of national health insurance claims in Taiwan found that people with T2DM had a higher incidence of epilepsy than controls independent of severe hypoglycaemia [21]. A Bosnian retrospective study found an association of early and late seizures with T2DM after stroke [22]. Another study also found an increased risk for epilepsy in people with T2DM [11, 23]. A review confirmed the association between epilepsy and T2DM [24]. Discussions of why this association exist are, however, very incipient. We examine possible drivers for the comorbidity of epilepsy and T2DM in an attempt to elucidate the possible biological mechanisms underlying the development of processes in individuals.

2. Materials and Methods

2.1. Scoping Review

We carried out a scoping review, used when a narrow review question cannot be determined. Scoping reviews are also useful when studies have employed diverse data collection and analysis methodologies, when no prior synthesis on the topic has been conducted, and the quality of the studies is not assessed [25].

2.2. Search Strategy

One of the authors (NS) conducted a search of PubMed and Medline up to December 2019. Search terms were determined after an initial exploration of the literature. These included epilepsy, comorbidity, comorbidities, type 2 diabetes, obesity, and antiepileptic. Boolean operators were also used to combine keywords. There were no language or study design restrictions.

2.3. Article Screening and Criteria

Titles and abstract were categorized as relevant or irrelevant. The full text judged as relevant were then evaluated by the reviewer. Articles were included if they were quantitative or qualitative peer-reviewed reports of studies focused on comorbidity of epilepsy with T2DM or obesity, antiseizure medication (ASM) and T2DM or obesity, or the factors associated with

these conditions; and examined biological mechanisms and/or associations between comorbid conditions.

2.4.   Data Extraction

Extracted data included the topic, purpose, and type of the study; demographic or other pertinent characteristics; the intervention, if any; the outcomes measured or the processes discussed; and the authors' conclusions.

2.5.   Data Synthesis

Articles were grouped according to topic. Within each group, numerical data were organized together, and descriptions of biological mechanisms were amalgamated from descriptions in the individual articles.

3.   Results

Initially, 3,361 articles were identified on PubMed. The keywords were rearranged for greater specificity by including only articles referencing either epilepsy or antiseizure medications along with at least one of T2DM, obesity, and exercise. This still yielded 1,008 articles. An analogous search strategy was employed for Medline, yielding 851 articles (Table 1). Additional searches were made if more information was required on a given topic. Articles were excluded if they did not focus on the comorbidity of epilepsy with T2DM or obesity, factors associated with epilepsy and T2DM or obesity, the effect of antiseizure medication use on factors associated with T2DM or obesity, or cellular or molecular mechanisms associated with either of the three above-mentioned conditions. They were also excluded if the articles were not in peer-reviewed journal, if the abstract or full text could not be sourced, or if they were duplicates. Ultimately, 82 articles were included (Figure 1). These sources included preclinical experiments (n=7), case reports (n=2), correlational studies (n=13), human subjects' experiments (n=25), and reviews (n=35).

4.   Discussion

4.1.   Epilepsy and Obesity

An US epidemiological study of a nationally-representative sample of people with epilepsy found adults with any epilepsy (34.1%) and inactive epilepsy (40.3%) were more likely to be obese than adults without epilepsy (27.5%) [7]. This study suggested a possible correlation between epilepsy, and obesity in adults.

A population-based study of children with epilepsy treated at a hospital in Ohio between 2003 and 2006 found children with epilepsy were more likely to be obese than those without [26]. Children with epilepsy who were older, had idiopathic epilepsy, or had no concomitant medication were more likely to be obese than other children with epilepsy [26]. This study suggested a correlation between epilepsy and obesity in children.

A Brazilian cross-sectional study of elderly people whose seizures began over the age of 51 determined that elderly people with new-onset epilepsy had greater waist circumference, indicative of greater levels of abdominal obesity [27]. This suggested a correlation between development of epilepsy and abdominal obesity in elderly people.

These studies show that epilepsy is frequently comorbid with obesity in children and adults. Possible drivers responsible for the comorbidity of epilepsy and obesity were not discussed in any of the reports [7, 26].

4.2. Obesity and T2DM

A review of weight issues in people with epilepsy found that 61% of the prevalence of T2DM is attributable to obesity and the risk of T2DM doubles with a gain of 5-8 kg of weight [28]. The likely molecular mechanisms behind T2DM suggest that it is characterized by two main features: insulin resistance and the dysfunction of pancreatic islet β-cells [29, 30]. Progression from normal glucose tolerance to impaired glucose tolerance is associated with an increase in body weight, decrease in insulin-stimulated glucose disposal, and decrease in the acute insulin secretory response to intravenous glucose. A longitudinal study of Pima Indians demonstrated that the progression from impaired glucose tolerance to diabetes is associated with a further increase in body weight, additional decreases in insulin-stimulated glucose disposal and the acute insulin secretory response [31].

In obese individuals, adipose tissue releases greater amounts of factors such as non-esterified fatty acids, glycerol, hormones, and pro-inflammatory cytokines than in non-obese individuals; triglyceride storage is impaired; and lipolysis is increased [29, 32]. All of these contribute to an increase in circulating fatty acid levels and promote an overload of fatty acids in skeletal muscle and the liver, causing decreased responsiveness of these tissues to insulin in obese individuals [30]. Eventually, this results in insulin resistance [32].

Pancreatic islet β-cells compensate for insulin resistance by hypersecreting insulin to maintain normoglycemia [33]. T2DM develops in people for which the β-cell compensatory insulin hypersecretion falters [33]. Insulin levels decrease when fasting glycemia exceeds the upper limit of normal glycemic levels of 5.5 mM, indicative of β-cell failure [34]. β-cell function is a major determinant of oral glucose tolerance and stimulates the progression from normoglycemia to diabetes [30].

4.3. ASM Studies in People with Epilepsy

Studies investigating the physiological effects of antiseizure medication are informative. The enzyme inhibitor valproic acid (VPA) as treatment for epilepsy was associated with weight gain in 50% of treated women which was associated with hyperinsulinemia [35]. VPA induced a metabolic syndrome consisting of centripetal obesity, hyperinsulinemia, lipid abnormalities, polycystic ovaries, and hyperandrogenism [36]. In a study comparing VPA with the enzyme inducer carbamazepine (CBZ), postprandial insulin and proinsulin levels were significantly higher for people treated with VPA than for people treated with CBZ, while no differences were found in the fasting state [37]. Replacing VPA with lamotrigine (LTG) reduced body mass index (BMI) and fasting serum insulin and testosterone concentrations and increased high density lipoprotein cholesterol to total cholesterol ratios [36]. Levels of these compounds returned to normal within two months of starting LTG [36].

A study of people with epilepsy treated with topiramate for one year found that up to 86% had reductions in baseline weight at 1 year [38]. Obese people had higher reductions in baseline weight than those non-obese [38]. Apart from its original antiseizure properties, topiramate has been used as a weight loss drug. It was found to decrease blood glucose levels

by 16% and insulin levels by 24%, in obese individuals but had no effect on serum glucose, insulin or triglyceride levels in non-obese people [39]. Overall, topiramate led to the largest weight loss in people with a high BMI [40]. In people with T2DM, weight loss and BMI reduction were higher in the topiramate treatment group than in controls [41]. These studies suggest baseline BMI predicts weight loss after topiramate treatment, particularly in people with epilepsy.

4.4. Role of Exercise

People with epilepsy are less likely to engage or even intend to engage in physical activities [42-44]. In a Norwegian sample, the proportion of people never exercising was significantly greater for an epilepsy cohort than the average population [45]. The physiological parameter of interest is the modifiable risk factor cardiorespiratory fitness, which is lower in people with epilepsy than age and gender-matched controls [46]. People with epilepsy have often been discouraged from partaking in physical activity due to concerns about inducing or increasing the frequency of seizures [43]. Similarly, interventions designed to increase exercise in people with epilepsy often fail to initially increase exercise or sustain increased exercise [47]. Reduced levels of exercise in people with epilepsy may result from depression, anxiety, perceived stigma, or the side effects of epileptic drugs [48].

Preclinical and human studies have shown that exercise is beneficial for people with epilepsy. In rat models of temporal lobe epilepsy and absence epilepsy, the exercise group experienced a significant reduction in seizure frequency compared to controls and sham groups [49, 50]. Studies conducted using a rat pentylenetetrazole model determined that exercise decreased seizure susceptibility, frequency, and latency [51, 52].

In a human trial, fifteen women with drug-resistant epilepsy engaged in aerobic dancing with strength training and stretching for one hour twice weekly for 15 weeks [53]. The frequency of self-reported seizures significantly decreased during the exercise intervention period [53]. A Chinese study using an intervention consisting of a low glycaemic diet and structured exercise decreased seizure frequency in children with refractory epilepsy [54]. A randomized control trial found physical activity decreased seizure frequency in children with epilepsy aged 8-14 [55]. This may result physiologically from reduced epileptic discharges during exercise [56], providing neuroprotective effects such as improved seizure control and improved cognitive function [57-61].

Exercise also affects the onset of epilepsy. A Swedish cohort study examining individuals initially free of epilepsy who participated in the cross-country Vasaloppet ski race compared to non-participating matched controls found that exercise decreased the incidence of epilepsy, indicating physical activity may delay or prevent epilepsy [62]. The intensity of exercise inversely correlated with incidence of epilepsy [62]. Lack of exercise may initially predispose people to epilepsy, and continued lack of exercise may allow for continued occurrence of seizures.

4.5. Mitochondrial Dysfunction

Mitochondrial dysfunction is common to epilepsy, obesity, and diabetes. Epilepsy is a neurological and systemic disorder resulting from fundamental pathophysiological processes [63]. Mitochondrial dysfunction is one of these processes and is linked to epilepsy through

changes in ATP production, calcium homeostasis, and oxidative stress by reactive oxygen species (ROS) [64]. Mitochondrial oxidative phosphorylation is the primary source of ATP production in neurons [65]. Mutations in mitochondrial DNA or nuclear genes resulting in impairment of the respiratory chain or mitochondrial ATP synthesis, are associated with epilepsy [66]. People with respiratory chain dysfunction may have epilepsy associated with an encephalopathy. As an example of a mitochondrial encephalopathy, deficiency of monosialodihexosylganglioside (GM3) synthase, an enzyme involved in the synthesis of complex gangliosides, results in secondary respiratory chain dysfunction and early-onset epilepsy [67]. Mitochondria are also involved in cellular calcium homeostasis [65]. Deficiencies in proper calcium regulation are associated with epilepsy [64]. Mitochondria are also the main site of ROS production, making them vulnerable to oxidative stress [68, 69]. Dysfunction resulting from oxidative stress promotes neuronal hyperexcitability by decreasing membrane potential and reducing network inhibition and alters synaptic transmission by damaging ion channels and neurotransmitter transports, all of which increase seizure susceptibility [64, 65, 68-70]. High oxidative status is associated with severity and recurrence of epileptic seizures [71]. Mitochondrial dysfunction also triggers neuronal cell death, a hallmark of drug-refractory epilepsy [65]. In mesial temporal lobe epilepsy with hippocampal sclerosis, progressive loss of pyramidal cells in the CA1, CA3, and CA4 layers occurs, correlated with impairment of respiratory chain complex I activity [72].

Seizures acutely necessitate excessive energy from the brain and are a manifestation of impaired mitochondrial energy production [64, 72]. Molecularly, this is associated with a decreased phosphocreatine/adenosine triphosphate (PCr/ATP) ratio [72]. The ketogenic diet has been associated with improved mitochondrial energy production via upregulation of mitochondrial genes and increased mitochondrial biogenesis in animal models [72]. In a MR-spectroscopy study of people with intractable epilepsy, the ratio of PCr/ATP and PCr/Pi significantly increased after a ketogenic diet compared to baseline, indicating an improvement in cerebral energy metabolism [72]. A calorie-restricted diet is less restrictive than a ketogenic diet but may reduce seizure frequency by improving mitochondrial energy production in the same way as a ketogenic diet [73]. It has also been hypothesized that pharmacoresistance and the subsequent likelihood of seizure recurrence results from the interplay of the seizuregenic potential of the epileptic focus, efficacy of ASMs, and mitochondrial dysfunction [72]. Preclinical and clinical studies are necessary to validate this hypothesis.

Mitochondrial dysfunction is linked to obesity and T2DM through its effects on ATP production, calcium homeostasis, and ROS generation [74-78]. Rates of mitochondrial oxidative phosphorylation in skeletal muscle were 30% less in insulin-resistant individuals than in controls [72]. suggesting deficiencies in mitochondrial ATP production [75]. In obese human and animal models, deficiencies in calcium homeostasis in the liver, adipocytes, and macrophages occur due to increased physical interaction and functional coupling between the endoplasmic reticulum and mitochondria and calcium transport [76]. Excessive caloric intake increases ROS production [74]. These factors allow for the development of obesity and T2DM. Mitochondrial dysfunction in T2DM leads to insulin resistance through deficiencies in insulin responsiveness of skeletal muscle and liver, mainly due to lower mitochondrial biogenesis and possibly reduced functional capacity per mitochondrion [75, 77, 79]. In an obese rat model, hepatic mitochondrial dysfunction preceded insulin resistance [73]. Insulin resistance results from dysregulation of

fatty acid metabolism in muscle cells through lack of ATP production and dysregulation of calcium homeostasis [75, 76]. Mitochondrial dysfunction also leads to dysfunction of pancreatic islet β-cells through increased lipid levels, hyperglycemia, and obesity [77]. ROS accumulation blocks fatty acid oxidation, resulting in lipid accumulation [74]. ROS accumulation also leads to deficiencies in glucose metabolism, namely insulin resistance in 3T3L1 pre-adipocytes [74]. Mitochondrial dysfunction leads to epilepsy, obesity, and T2DM through the same general mechanisms. Exercise reduces mitochondrial dysfunction [80-82], and may be protective against epilepsy, obesity, and T2DM.

4.6. Adiponectin Deficiency

Adiponectin stimulates fatty acid oxidation and glucose uptake in skeletal muscle [83], Epilepsy is associated with adiponectin deficiency through the anti-inflammatory effects and wide-ranging CNS effects of adiponectin [84]. People with temporal lobe epilepsy may have lower circulating adiponectin levels than healthy people [84]. Epilepsy duration in temporal lobe epilepsy seems inversely associated with adiponectin plasma levels [84]. Adiponectin increases within 24 hours of tonic-clonic seizures but decreases in the interictal period, indicating the presence of a brief anti-inflammatory state within the setting of a persistent pro-inflammatory condition [84, 85]. The immediate rise in adiponectin levels following convulsions presumably occurs to prevent deleterious CNS effects [85]. Continuous activation of the CNS, particularly astrocytes and microglia, secondary to long-term adiponectin deficiency may enhance local and systemic inflammatory mechanisms [84].

Adiponectin deficiency also often occurs after ASM treatment. In a study of people treated with VPA, about a third developed obesity, exhibiting circulating insulin levels significantly higher and adiponectin levels significantly lower than those who did not gain weight [86]. Overweightness associated with VPA is accompanied by lower adiponectin levels [87]. Similarly, treatment with VPA predisposed obese children with idiopathic epilepsy to insulin resistance and lower adiponectin levels compared to age and gender matched obese controls [88]. VPA also induced hypoadiponectinemia and insulin resistance in previously untreated people with epilepsy [89, 90]. Other studies, however, have found non-significant increases in adiponectin levels after VPA treatment [91, 92]. Children with epilepsy treated with topiramate showed increased serum levels of adiponectin and weight loss, suggesting the association between levels of adiponectin and weight loss mediated by topiramate [93].

Low plasma adiponectin levels are associated with obesity and T2DM [83, 94]. The degree of hypoadiponectinemia is most closely associated with the degree of insulin resistance and hyperinsulinemia [89, 93]. The presence of insulin resistant previously untreated females with epilepsy indicates that weight gain itself may not cause insulin resistance [89], but rather that adiponectin deficiency may promote insulin resistance and weight gain. While R112C, 1164T, R221S, and H241P are missense mutations in adiponectin, the frequency of the 1164T mutation is significantly higher in people with T2DM than controls, and all subjects with the 1164T mutation had T2DM [95].

A preclinical study has suggested a possible connection between epilepsy, obesity, and T2DM involving adiponectin deficiency. Mice with adiponectin deficiency fed a high-fat diet had greater fat accumulation, hyperlipidemia, impaired glucose tolerance, and increased kainic acid-induced seizure severity [96]. A lack of adiponectin has systemic effects, precipitating all three

conditions. Exercise increases adiponectin levels in preclinical and human studies [97-102], and may be protective against epilepsy, obesity, and T2DM.

4.7.   *Proposed Mechanisms for Development of T2DM in People with Epilepsy*

One possible mechanism that we propose for the development of T2DM in people with epilepsy is that mitochondrial dysfunction [63-79] and adiponectin deficiency [83-102] predispose people to epilepsy, obesity, and diabetes. The same biological drivers underlie each of these three conditions due to the systemic nature of both these drivers and the conditions. Inadequate exercise can contribute to these biological drivers [80-82, 97-102]. Temporally, the precise sequence of comorbidity development may be highly individualized: some people may develop epilepsy and then T2DM or vice versa. The degree of mitochondrial dysfunction and adiponectin deficiency and local and systemic contributions of these drivers relative to each other may underlie which condition develops first.

Another possible mechanism is that people with epilepsy are more likely to be obese as they exercise less [43, 45, 49, 53]. They are also more likely to be obese if treated with VPA [35-37], contributing to mitochondrial dysfunction and adiponectin deficiency. Obesity, in turn, predisposes them to T2DM [28]. Mitochondrial dysfunction and adiponectin deficiency develop in people with obesity as they continue living with the condition. These pathophysiological processes may become apparent prior to development of T2DM in people with epilepsy, and their further progression may precipitate T2DM.

A third possible mechanism is that, at baseline, people with epilepsy have greater mitochondrial dysfunction and lower adiponectin levels than people without epilepsy, and treatment with ASMs lowers adiponectin levels and increases mitochondrial dysfunction further compared to people without epilepsy [64, 72, 84, 87-93]. Mitochondrial dysfunction and adiponectin deficiency in people with epilepsy precipitate the development of obesity, T2DM, or both conditions. Whether people develop obesity, T2DM, or both and the time elapsed between epilepsy onset and development of these conditions may depend on the absolute or relative degrees of mitochondrial dysfunction and adiponectin deficiency.

All three mechanisms are likely involved in the comorbidity of epilepsy and T2DM. The shared biological drivers of epilepsy and T2DM may occur either sequentially or concurrently. More research is warranted to determine factors associated with each of these mechanisms.

5.   Conclusions

The association between epilepsy and T2DM is not yet clear and suffers from a lack of epidemiological evidence and sustained biomedical research efforts. We propose three possible mechanisms for the comorbidity of epilepsy and T2DM. One mechanism is that mitochondrial dysfunction and adiponectin deficiency promote epilepsy, obesity, and T2DM. The degree of each of these pathogenic changes determines which condition develops first. Another mechanism is that people with epilepsy are more likely to be obese due to lack of exercise and the effects of some ASMs, which makes them susceptible to T2DM due to the development of mitochondrial dysfunction and adiponectin deficiency. A third mechanism is that people with epilepsy have greater mitochondrial dysfunction and lower adiponectin levels than people without epilepsy at baseline, which is exacerbated after treatment with ASMs. The absolute or

relative degrees of mitochondrial dysfunction and adiponectin deficiency may affect whether and when people develop obesity, T2DM, or both conditions.

More work is required to determine the precise association between epilepsy and T2DM and whether these proposed mechanisms are valid. One technique that can be used to accomplish this is genome-wide association studies. Genome-wide association studies have characterized genes involved in the development of T2DM [103-107]. Screening for epilepsy and T2DM will be useful in delineating genes implicated in both conditions. Genome-wide association studies likely to be complicated by the interactions of different combinations of loci in epilepsy, which produce pathogenic and clinical heterogeneity [108]. Another technique is exhaustively characterizing the molecular pathways resulting in each condition [109]. This technique, however, provides only indirect evidence for comorbidities as it relies on molecular interaction networks [109], which are often difficult to elucidate. A novel approach integrating genetic information and high-level molecular changes has demonstrated strong consistency with known comorbid disease [109]. Using a combined genetic and molecular pathway approach for epilepsy and T2DM will likely yield valuable insight regarding the comorbidity of these conditions.

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Figure Legends

Figure 1: Study selection flowchart for the epilepsy and T2DM scoping review.

Table 1: Search strategy

Database	Search Strategy	Number of Articles
PubMed – first attempt	("epilepsy"[TIAB] OR "antiepileptic"[TIAB]) AND ("comorbidity"[TIAB] OR "comorbidities"[TIAB] OR "type 2 diabetes"[TIAB] OR "obesity"[TIAB] OR "obese"[TIAB] OR "exercise"[TIAB])	3,361
PubMed – second attempt	"epilepsy comorbidity"[TIAB] OR "epilepsy comorbidities"[TIAB] OR ("epilepsy"[TIAB] AND "exercise"[TIAB]) OR ("epilepsy"[TIAB] AND "type 2 diabetes"[TIAB]) OR ("epilepsy"[TIAB] AND "obesity"[TIAB]) OR ("antiepileptic"[TIAB] AND "exercise"[TIAB]) OR ("antiepileptic"[TIAB] AND "obesity"[TIAB]) OR ("antiepileptic"[TIAB] AND "type 2 diabetes"[TIAB])	1,008
Medline	("epilepsy comorbidity" or "epilepsy comorbidities" or ("epilepsy" and "exercise") or ("epilepsy" and "type 2 diabetes") or ("epilepsy" and "obesity") or ("antiepileptic" and "exercise") or ("antiepileptic" and "obesity") or ("antiepileptic" and "type 2 diabetes")).ti,ab,cl,oa,kw,kf.	851

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┌─────────────────────────┐   ┌─────────────────────────┐
│ Records identified      │   │ Records identified      │
│ through primary         │   │ through additional      │
│ database queries        │   │ queries                 │
│ (n = 1,859)             │   │ (n = 337)               │
└───────────┬─────────────┘   └───────────┬─────────────┘
            │                             │
            └──────────────┬──────────────┘
                           ▼
              ┌─────────────────────────┐
              │ Records identified      │
              │ through database        │
              │ searches                │
              │ (n = 2,196)             │
              └───────────┬─────────────┘
                          │          ┌─────────────────────────┐
                          ├─────────►│ Duplicates excluded     │
                          │          │ (n = 831)               │
                          ▼          └─────────────────────────┘
              ┌─────────────────────────┐
              │ Records screened by     │
              │ title and abstract      │
              │ (n = 1,365)             │
              └───────────┬─────────────┘
                          │          ┌─────────────────────────┐
                          ├─────────►│ Records excluded on     │
                          │          │ basis of title and      │
                          │          │ abstract (n = 1,106)    │
                          ▼          └─────────────────────────┘
              ┌─────────────────────────┐
              │ Full text records       │
              │ assessed by eligibility │
              │ (n = 259)               │
              └───────────┬─────────────┘
                          │          ┌─────────────────────────┐
                          ├─────────►│ Records excluded        │
                          │          │ (n = 177)               │
                          ▼          └─────────────────────────┘
              ┌─────────────────────────┐
              │ Records included in     │
              │ review                  │
              │ (n = 82)                │
              └─────────────────────────┘
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