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Risk factors for frontotemporal dementia

REVIEW ARTICLE

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BACKGROUND

Risk factors for frontotemporal dementia are poorly understood. The purpose of this article is to provide an up-to-date review of modifiable risk factors for frontotemporal dementia and to evaluate the evidence base for clinical recommendations on how to reduce risk.

METHOD

Searches were performed in the PsychInfo, Embase, PubMed and Cochrane databases in the period May 2016 to April 2017. The search yielded 137 articles, of which 101 were excluded because they concerned only genetic aspects of frontotemporal dementia and non-modifiable risk factors. After reading 36 articles in full, we selected 12 articles that were either reviews or original studies.

RESULTS

Some studies showed an association between modifiable risk factors and the development of frontotemporal dementia. One study found that diabetes gives rise to increased risk. Three studies showed that head injury can increase the risk of frontotemporal dementia and that the prevalence of traumatic brain injury is significantly higher in patients with frontotemporal dementia than with other forms of dementia. Autoimmune disease may be associated with increased risk of primary progressive aphasia, a subtype of frontotemporal dementia.

INTERPRETATION

The literature suggested an association between diabetes, head injury, autoimmune disease and frontotemporal dementia. There is currently insufficient evidence on which to base recommendations for lifestyle changes to prevent frontotemporal dementia at the population level.

The umbrella term *frontotemporal dementia* encompasses several neurodegenerative diseases that lead to neuronal loss in the frontal and/or temporal lobes (1). Frontotemporal dementia can be divided into two phenotypic groups on the basis of changes in either behaviour or language. The behavioural variant accounts for about half of all cases and includes changes in behaviour and personality (2). This variant is characterised by focal and prominent frontal atrophy. The language variant is called primary progressive aphasia and consists of three subtypes: a non-fluent variant (known as progressive non-fluent aphasia), a semantic variant (known as semantic dementia) and a logopenic variant (known as logopenic aphasia) (3–5). The semantic variant is characterised by bilateral anterior temporal lobe atrophy and is associated with language difficulties, compulsions and impaired emotional processing (3). Frontotemporal dementia overlaps with other neurodegenerative diseases such as progressive supranuclear palsy, corticobasal degeneration and behavioural variant frontotemporal dementia with motor neuron disease (6) (Box 1).

Box 1 Frontotemporal dementia

Term encompasses the following disorders (3–6):

1. Behavioural variant. Accounts for about half of all frontotemporal dementia cases and includes altered behaviour and personality
2. Language variant (primary progressive aphasia). Consists of three subtypes:
    - Non-fluent variant (progressive non-fluent aphasia)
    - semantic variant (semantic dementia)
    - logopenic variant (logopenic aphasia)

Frontotemporal dementia also overlaps with other neurodegenerative diseases:

- Progressive supranuclear palsy
- Corticobasal degeneration
- Behavioural variant of frontotemporal dementia with motor neuron disease

Many patients with frontotemporal dementia show symptom onset in their fifties or sixties, with some individuals affected as early as their thirties or forties (7). The interval between symptom onset and diagnosis may be up to five years (8, 9), and there is currently no curative treatment (10). Risk factors for dementia can be divided into modifiable and non-modifiable (11). Knowledge of modifiable risk factors is important for clinicians who wish to offer patients advice on how to prevent or reduce the risk of developing dementia.

Frontotemporal dementia is one of the most common forms of dementia in those under the age of 65 (4), and is thought to account for about 10 % of all cases in this age group (12). The prevalence of dementia under the age of 65 in Norway has been estimated at 1 200–1 400 cases, but up-to-date figures are not available for incidence and prevalence among younger persons (8). A family

history is one of the major risk factors for frontotemporal dementia, but up to 60 % of those affected have no known family members with the condition (13). This indicates that 6 out of 10 cases are sporadic (non-hereditary) (13). Frontotemporal dementia is linked to chromosome 17 in some families, with an autosomal dominant inheritance pattern, and to chromosomes 3 and 9 in other cases. Mutations in the tau gene have also been detected in certain cases (14). Knowledge of modifiable risk factors for frontotemporal dementia can therefore play a key role in understanding who is affected.

The purpose of this article is to provide an up-to-date review of modifiable risk factors for frontotemporal dementia and to evaluate whether the evidence base is sufficient to provide clinical recommendations aimed at reducing risk.

Method

We conducted a systematic search in the PsychInfo, Embase, PubMed and Cochrane databases, using the MeSH terms and keywords 'frontotemporal degeneration', 'frontotemporal dementia', 'frontotemporal lobar degeneration', 'dementia', and 'risk factors'. The search was limited to articles published in the period 1 January 2005 to 24 January 2017. The search was filtered by the following languages: Norwegian, Danish, Swedish and English.

The inclusion criteria were that articles should be reviews or original studies with data on modifiable risk factors for frontotemporal dementia. Studies of non-modifiable risk factors as well as all case reports, opinion pieces and conference proceedings were excluded. The search yielded 137 articles, of which 101 were excluded because the title revealed that they were not about modifiable risk factors. A total of 36 articles were read in full, of which a further 25 were excluded because they did not relate to modifiable risk factors. The 11 articles included were all either review articles or original studies with data on modifiable risk factors for frontotemporal dementia. An article from the reference list of one of the 11 was included in addition, bringing the total to 12 articles (Figure 1, Table 1) (13), (15–22).

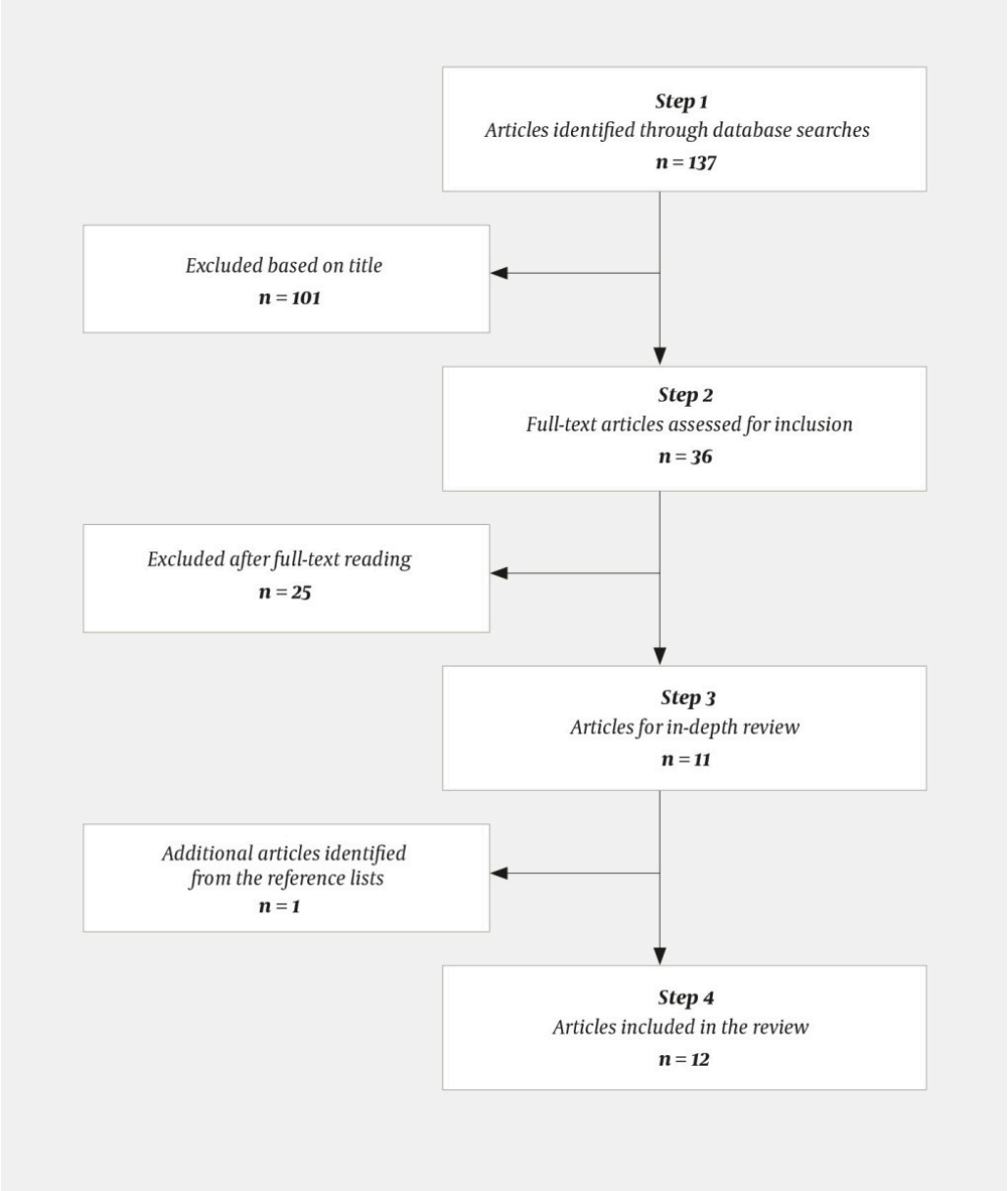

Figure 1 Flow chart for the literature search

Table 1

Risk factors for frontotemporal dementia (FTD) in the studies selected

Study	Country	Setting	Sample	Main finding
De Reuck, 2012 (15)	France	A memory clinic and a hospital	22 brains from deceased persons diagnosed with FTD *Control group:* 15 brains from deceased persons with no history of brain disease	Cerebrovascular risk factors and lesions were less common among persons with FTD, whereas changes in white matter were more prevalent and more severe

Study	Country	Setting	Sample	Main finding
Golimstok, 2014 (16)	Argentina	Hospital	100 persons with FTD *Control group* 200 persons without dementia or any other neurological disease	Diabetes was identified as a risk factor for FTD.
Kalkonde, 2012 (17)	USA	Memory clinic	63 patients with behavioural variant FTD *Control group:* 491 patients with another form of dementia	Patients with FTD had a higher prevalence of traumatic brain injury and lower prevalence of cardiovascular disease and cerebrovascular disease than the control group.
Torralva, 2015 (18)	USA	Hospital	62 patients with behavioural variant FTD and cerebrovascular disease *Control group:* 329 patients with behavioural variant FTD without cerebrovascular disease	The FTD group was older at disease onset and had more cases of stroke and hypertension than the control group.

Study	Country	Setting	Sample	Main finding
Borroni, 2008 (19)	Italy	Hospital	117 patients with FTD *Control groups:* 400 patients with Alzheimer´s disease 55 patients with progressive supranuclear palsy 55 patients with corticobasal degeneration	The FTD patients: • were younger than the control groups with Alzheimer's disease and progressive supranuclear palsy. • had a stronger family history of dementia than the patients with Alzheimer's disease. • had a higher prevalence of *APOE*-risk genotype than the control groups with corticobasal degeneration and progressive supranuclear palsy. • had a higher educational level than the control group with Alzheimer's disease. • had a lower prevalence of cardiomyopathy and hypertension than the control group with Alzheimer's disease. • had a lower prevalence of hypertension than the control group with progressive supranuclear palsy.
Rosso, 2003 (13)	Netherlands	Hospital	80 patients with sporadic FTD *Control group:* 124 patients without cognitive impairment or dementia	The FTD patients had a higher prevalence of head injury and metabolic disease than the control group.

Study	Country	Setting	Sample	Main finding
Miller, 2013 (20)	USA	Academic medical centre	129 patients with the semantic variant of primary progressive aphasia *Control groups:* 39 patients who were progranulin mutation carriers 186 patients with normal cognition 158 patients with Alzheimer's disease	The FTD patients and the control group of progranulin mutation carriers had an increased prevalence of certain autoimmune diseases compared to the control groups with normal cognition or Alzheimer's disease.
Deutsch, 2015 (21)	USA	Academic medical centre	1 016 patients with FTD *Control group:* 2 015 patients without cognitive impairments	Head injury with loss of consciousness was more common in patients with FTD than in the control group.
Atkins, (2012) (22)	Australia	Research centre	62 persons with early Alzheimer's disease *Control group:* 61 persons with early FTD	There were more smokers and individuals with higher body weight among patients with FTD than in the control group with early Alzheimer's disease.

The literature review was performed in accordance with the PRISMA criteria (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (23).

Education

A high educational level is considered to be protective against Alzheimer's disease and vascular dementia (19). The relationship between educational level and frontotemporal dementia, progressive supranuclear palsy and corticobasal degeneration has also been examined (19). The analysis included risk factors such as family history, cardiomyopathy, hypertension, hypercholesterolaemia, diabetes and apolipoprotein genotype, and was adjusted for age and gender. The analysis compared 117 patients with frontotemporal dementia with control groups comprising 400 patients with Alzheimer's disease, 55 with primary supranuclear palsy and 55 with corticobasal degeneration. The results revealed that persons with frontotemporal dementia were on average younger at disease onset, had higher levels of education and were more likely to have family members with dementia than the control groups (19).

Cardiovascular risk factors

Another study from 2014 found that approximately 60 % of patients with frontotemporal dementia were sporadic cases (16). The study included 100 patients with frontotemporal dementia and a control group of 200 persons. After adjusting for gender, age, diabetes, hypertension, overweight, dyslipidaemia, hypothyroidism and osteoporosis, a significant association was found between frontotemporal dementia and type 2 diabetes compared with the control group. Type 2 diabetes was shown to be an independent risk factor for frontotemporal dementia (16).

In 2015, researchers found that it was more difficult to diagnose frontotemporal dementia in persons who had previously had a stroke (18). Patients with the behavioural variant of frontotemporal dementia more often had hypertension and a history of stroke. The findings of this study suggest that cerebrovascular disease should not be ruled out in cases of behavioural variant frontotemporal dementia (18).

Another prospective study found that persons with early Alzheimer's disease had an almost three times greater risk of hypertension than those with early frontotemporal dementia, whereas smoking and overweight were more common in the group with early frontotemporal dementia (22). With the aid of 22 brain biopsies, researchers found that cerebrovascular lesions were less common in persons with frontotemporal dementia compared with healthy control subjects, but that white matter changes occurred more often. These should therefore not be used in isolation as a prognostic indicator (15).

Head injury

Head injury was associated with an increased risk of frontotemporal dementia, with an odds ratio of 3.3 in a cohort of 80 patients with sporadic frontotemporal dementia versus a control group of 124 persons without cognitive impairment (13).

In another study, a cohort of 63 patients with behavioural variant frontotemporal dementia was compared to a control group of 491 patients with another form of dementia. Traumatic brain injury was found to be more common in the patients with frontotemporal dementia (17).

A major study that included 1 016 persons with frontotemporal dementia and a control group of 2 015 persons without cognitive impairment showed that head injury with loss of consciousness was more common in patients with frontotemporal dementia and may increase the risk of the disorder (21).

Autoimmune disease

One study has shown an increased prevalence of specific autoimmune diseases in patients with the semantic variant of primary progressive aphasia and in progranulin mutation carriers compared to healthy control subjects and control subjects with Alzheimer's disease (20).

Discussion

Our literature review demonstrates that few studies have examined modifiable risk factors for frontotemporal dementia (4, 5). It is important to note that early symptoms of frontotemporal dementia may include impulsive and disinhibited behaviour leading to, for example, hyperorality, with increased consumption of carbohydrate-rich foods in particular, or increased use of alcohol and tobacco (1, 3). Little is known about the length of the prodromal phase in frontotemporal dementia, but studies show that it may take up to five years from the initial examination for a diagnosis to be made (8).

The study showing that patients with frontotemporal dementia are younger and have higher educational levels than patients with Alzheimer's disease, used persons with other dementia disorders as controls. This may result in selection bias owing to differences in age of onset between the disorders (19). Another source of bias must also be considered: Higher education is more common among younger persons than among older generations, and frontotemporal dementia often affects younger individuals.

In terms of cardiovascular risk factors, a significant association was found between frontotemporal dementia and type 2 diabetes in one study (16), and between smoking, overweight and frontotemporal dementia in another (22). In case-control studies, overweight and smoking may be viewed as modifiable risk factors for frontotemporal dementia, but they may also form part of the prodromal phase.

There are conflicting findings in two studies regarding the status of hypertension as a risk factor: Kalkonde *et al.* found a fairly similar prevalence of hypertension in patients with frontotemporal dementia versus other forms of dementia (17), whereas Atkins *et al.*, who included a cohort of individuals with early-stage frontotemporal dementia and a control group with early-stage Alzheimer's disease, found hypertension to be more common in Alzheimer's disease (22). One reason for the divergent findings may be that one of the studies used a younger disease cohort and a younger control group.

Three studies show that head injury increases the risk of developing frontotemporal dementia. One of these studies featured a markedly larger disease cohort than all of the other studies we identified, with 1 016 persons with frontotemporal dementia (21). Head injury is thus the most studied risk factor, but two of the studies have small sample sizes and all three use different definitions of head injury. One study found an association between autoimmune disease and the semantic variant of primary progressive aphasia (20). This study includes no control variables in terms of other diseases or lifestyle variables, which should be considered a weakness. It is unclear whether there is an association between systemic autoimmune disease and frontotemporal dementia.

Conclusion

The literature suggests associations between diabetes, head injury and autoimmune disease, and frontotemporal dementia, but the current evidence base is too narrow to be able to draw any conclusions. There is insufficient

evidence to support recommendations for specific lifestyle changes aimed at preventing frontotemporal dementia at the population level.

One of the authors is an editor of Tidsskriftet. The manuscript has therefore been handled by external editor Jan Frich.

Main message

We found no studies that were able to show an effect of treatment in slowing or preventing the development of frontotemporal dementia

Head injury was the biggest risk factor for frontotemporal dementia among those examined in this study

Given that no treatment currently exists, there is a major need for more research on how to prevent frontotemporal dementia

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