Alzheimer's Disease & Treatment

Chapter 3

Alzheimer's Disease and Occupational Exposures: A Systematic Literature Review and Meta-Analyses

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Abstract

Six systematic literature reviews together with meta-analyses have been published on the associations between Alzheimer's disease and occupational risk factors. Our meta-analyses were based only on studies fulfilling good standards of scientific quality. We scrutinized the 54 relevant original publications found using a checklist proposed by the MOOSE-group together with a new elaborated protocol. Thus our results are not hampered by bias from studies of lower scientific quality. Thirty publications fulfilled good scientific standards and were thus used in our meta-analyses. Exposures to electromagnetic fields were concerned in 12 publications. The weighted relative risk estimate was 1.35 (95% confidence interval: 1.08-1.70). Exposure to pesticides or other chemicals resulted in the statistically significant relative risk 1.5 while exposure to metals involved no increase of risk. A high degree of work complexity (especially in relation to people) and long education were both protective against Alzheimer's disease. Based on ten studies the weighted relative risk was 0.47 (95% CI: 0.35-0.63). Both work-related risk factors and protective factors are discussed in relation to possible pathophysiological mechanisms.

Key words: Epidemiology; Electromagnetic fields; Pesticides; Chemicals, Metals; Work complexity; Education.

1. Introduction

Alzheimer's disease is both the predominant type of dementia and the most prevalent of the degenerative disorders. The disease is present in less than 1% of the population at age 65, but after that the prevalence doubles every fifth year [1]. Since the degenerative process starts decades before the onset of clinical disease, it is relevant to examine whether exposures at the workplace are risk or protective factors. There is evidence that some lifestyle factors are important to consider with regard to risk of Alzheimer's disease. Smoking exerts almost a doubled risk [2], while the effects of alcohol and diet are smaller and more complex [3,4].

Six systematic literature reviews have been published on associations between Alzheimer's disease and occupational risk factors [1,5-9]. Two of these publications also included meta-analyses with a focus on exposure to electromagnetic fields, and both studies indicated that exposure might involve an increased risk of disease [8,9] The results were quite heterogenic, which might be explained by methodological weaknesses in some of the included studies with regard to validity of diagnoses and exposures, statistical methods, and recall bias.

Our study originated in a commission from one of the biggest public insurance companies on the Swedish labor market (AFA Insurance), which needed a scientifically-based standard for evaluating work-related disease. The commission involved creating an updated foundation for decisions regarding prevention of and compensation for damage. Taking into consideration all work-related exposures with regard to Alzheimer's disease,we conducted a systematic review of the published literature, scrutinized relevant publications, and carried out meta-analyses using only studies that fulfilled good scientific standards. Our report was published in year 2015 in a Swedish peer-review scrutinized series of publications https://gupea.ub.gu.se/handle/2077/40542. The aim of the present chapter is to update our previous review and meta-analyses and to make the results available to the international public.

2. Methods

2.1. Literature Search

We identified relevant published articles using bibliographic search engines in PubMed, Embase, and Arbline prior to 1 February 2016. Our search criteria were MeSH terms for study design (*cohort, epidemiol*, epidemiologic studies*) in combination with MeSH terms for exposure (*employment, workplace, professions, career, career choice, job, occupations, employment, occupational health, occupational medicine, occupational exposure, occupational injuries, occupational diseases, electromagnetic field*) in combination with any of the MeSH terms for disease (*Alzheimer, Alzheimer disease*). This search produced 919 articles. After we scrutinized the titles and/or abstracts and excluded a few duplicates and excluded all articles

which were not based on original data on exposures related to occupation 89 potentially relevant articles remained.

2.2. Quality Classification

We assessed all relevant publications according to the checklist proposed by the MOOSE-group. [10] We considered selection bias and 'falling off [11], as well as occurrence of dose-response effects [12] and used a system for grading observational epidemiologic articles into a global class I-V as proposed by Armon. [13] Based on these documents, we constructed a decision protocol involving the categories Diagnosis, Exposure, Study group (selection, controls, missing data), Methods and analyses, Armon class, Funding and Exposures, see table 1 and 2. Armon's check-list and our decision protocol are presented in an appendix to a recent publication [14].

An appropriate diagnosis is a basic criterion for classification and preferably should fulfil the NINCDS-ADRDA consensus standards (National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association) used for a clinical diagnosis of Alzheimer's disease. [15] The NINCDS-ADRDA standards are compatible with the diagnostic criteria used both in Diagnostic and Statistical Manual of Mental Disorders (DSM III) and International Classification of Diseases (ICD 9).

The quality of the diagnosis was graded with scores from 1 to 4: 1=the Alzheimer's disease diagnosis from a specialist (neurologist/psychiatrist), 2=diagnosis from a hospital (as an in-patient), 3=diagnosis from a doctor (also including mortality registers), and 4=dementia without separation of Alzheimer's disease. The other categories were graded also with scores from 1 to 4: 1=good, 2=sufficient, 3=uncertain/insufficient, or 4=unacceptable. Sometimes a category was graded in between, and thus was given an interval, for example 2-3. The reason for this was usually lack of sufficient information to obtain a unique score.

The prerequisites for accepting a publication as fulfilling good scientific standards (Armon class II or III) were that the diagnosis score should be 1, 2 or 3 and all the other categories should be scored as 1-2, or 2-3. Articles not qualifying for classes II-III were impaired by serious weaknesses (Armon class IV) or should not be paid attention to (Armon class V). None of the publications fulfilled Armon class I, which almost requires an experimental design.

Only publications [5, 16-44] fulfilling good scientific standards (Armon class II or III) were used in our meta-analyses; see Table 1. Relevant publications not fulfilling good scientific standards regarding the exposure of interest [45-68] are summarized in Table 2.

2.3. Statistical Analysis

Risk estimates from the selected studies are reported as relative risks (RR), as the

outcome is rare, and so odds ratios (OR) and hazard ratios (HR) can be considered equivalent to the RR. When both unadjusted and multivariable-adjusted risk estimates were reported, we only considered the adjusted estimates. Studies which reported stratified estimates for sex were considered as separate studies, and included with both estimates. When exposure was categorized into different levels, the risk rate for the highest level was used according to the principle of dose-response, [69] provided a sufficient number of exposed cases was observed (usually around 30 or more). Estimates based on an extremely small number of individuals were not included, as their effect on the combined estimate could only be of an extremely small magnitude.

We examined the fixed effects model as well as the random effects model by considering statistical heterogeneity. To this end, we used the I^2 statistic and considered the recommended cut-offs of 25%, 50%, and 75% degrees of heterogeneity. We also used a meta-regression approach to stratify on study characteristics, selected a priori, and to evaluate the significance of the stratification variable. The I^2 criterion was applied to examine heterogeneity for each strata. As both these tests indicated a random effects model as the most appropriate choice in almost all studies, the results are reported with random effects estimates. Another reason to choose the random effects model was that the results were drawn from observational studies in different contexts, such as different countries and industries. The weights used for pooling the risk estimates were equal to the inverse-variance weighting. We also performed leave-one-out analysis for each study, to check the influence of each study on the combined estimate.

Publication bias was analyzed by inspection of the funnel plot, which in the absence of such bias would show the RR estimates distributed symmetrically around the weighted RR. The rank correlation test proposed by Begg & Mazumdar [70] was used to supplement the interpretation of the funnel plot. Statistical analyses were conducted using procedures for different aspects of meta-analysis available in STATA software (version 14.2, www.Stata.com), and described in articles from the STATA journal [71].

3. Results

3.1. Electromagnetic Fields and Work With Electricity.

Occupational exposure to electromagnetic fields and work with electricity has been studied extensively with regard to neurodegenerative diseases. Based on 14 publications of sufficient scientific standards, the weighted risk estimate for Alzheimer's disease was 1.25 with a 95% confidence interval (CI) of 1.07-1.46 **(Figure 1)** and for electromagnetic fields in particular the estimate from 12 publications was 1.35 (95% CI: 1.08 – 1.70). The estimate remained firm irrespective of different stratifications (study quality in grade II or III, design in case-control or cohort and funding in public funding or not). Between 1998 and 2014 the estimated cumulative risk rate gradually decreased from 2.70 to 1.25. The funnel plot **(Figure**

2) showed an asymmetric distribution which was especially evident for smaller studies with increased risk, but the risk estimates from more recent studies involving more cases were arranged fairly symmetrically around the combined estimate RR=1.25. Begg's test gave p=0.13, indicating some publication bias, but not to a very pronounced degree.

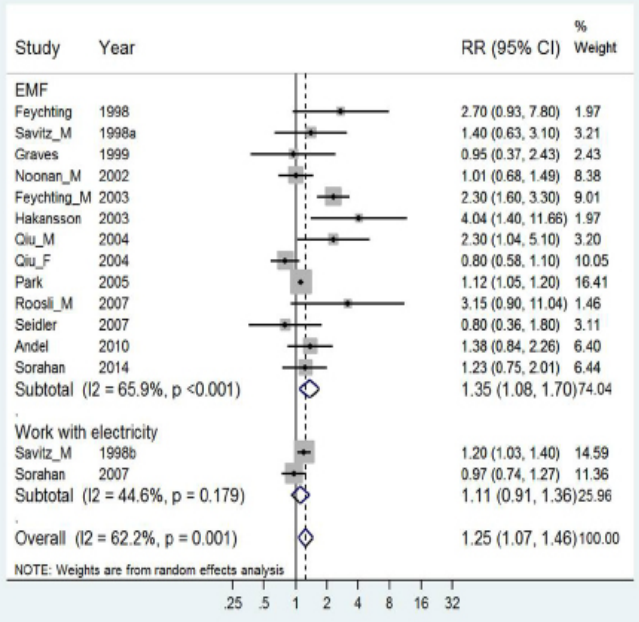

Figure 1: Forest plot for studies assessing the association between Alzheimer's disease and occupational exposure to electromagnetic fields and work with electricity. Results for men only are indicated by M and those for women only by F; otherwise the results concern both sexes. Random effect models were used, with stratification for different exposure categories. Heterogeneity was tested by the I^2 statistic, with $p<0.05$ indicating rejection of homogeneity.

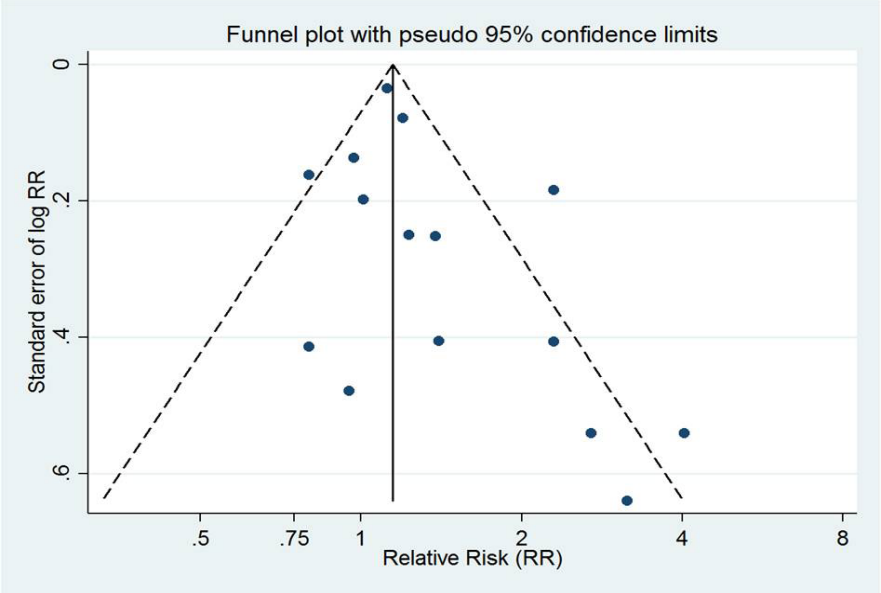

Figure 2: Funnel plot for the RR estimates of the association between Alzheimer's disease and exposure to electromagnetic fields and work with electricity.

The leave-one-out test showed that excluding the result from Feychting [20] for males had the greatest impact on the combined estimate, lowering it to 1.15 (95% CI: 1.01–1.31), and that excluding the large study by Park [32] raised the estimate to 1.32 (95% CI: 1.06–1.63). Also the heterogeneity as indicated by I^2 decreased from 62.2% to 41.8% when the result for Feychting was excluded, and a fixed effect estimate for RR was 1.13 (95% CI: 1.06 – 1.19),

thus somewhat lower risk and a smaller confidence interval.

3.2. Chemicals and Metals

The four publications on associations between Alzheimer's disease and exposure to chemicals [19,22,29,32] gave a weighted risk estimate of 1.52 (95% CI: 1.00–2.31) **(Figure 3)**. In one of these publications, the information on exposure was less specific, being based only on occupation as registered in the census [32]. Exclusion of this study yielded a weighted risk estimate of 1.93 (95% CI: 1.30-2.87) and no heterogeneity. The four publications concerning the effect of pesticide exposure [19, 25, 32, 35] gave a risk estimate of 1.50 (95% CI: 0.98–2.29) **(Figure 4)**. Excluding the study by Park [32] increased the estimate to 1.85 (95% CI: 1.12–3.05). Regarding chemicals and pesticides there were too few studies to make the tests of publication bias trustworthy. Three studies examined exposure to metals; aluminium [22] and welding [32, 43]. The weighted risk estimate for these diverse metal exposures was 0.95 (95% CI: 0.90–1.00) **(Figure 5)**. There was no heterogeneity and the study by Graves [22] had almost no influence on the weighted risk estimate.

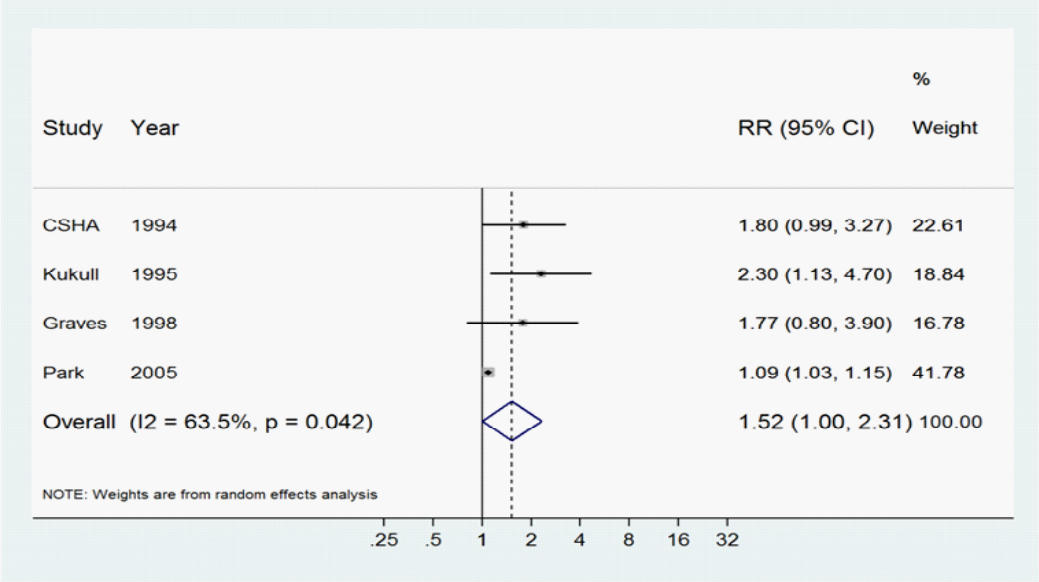

Figure 3: Forest plot for studies assessing the association between Alzheimer's disease and occupational exposure to chemicals. A random effect model was used. Heterogeneity was tested by the I^2 statistic, with $p<0.05$ indicating rejection of homogeneity.

3.3. Work complexity and education

Education level and work complexity were studied in twelve publications. [5,16,18,19,26-28,30,33,39,40,44] One of these publications was excluded from the meta-analyses, since it only stated that Alzheimer's disease was not associated with any specific occupation and did not present numeric risk estimates. [26] However, that study showed that the relative risk in the group with dementia (including Alzheimer's disease) was 0.66 (95% CI: 0.48-0.91) comparing white-collar work with blue-collar work. Another publication [40] was also excluded from the meta-analyses since the statistical methods were not analogous to the methods in the remaining

ten publications. However, that article stated that overall the cases showed significantly lower mental occupational demands and significantly higher physical occupational demands, in comparison to controls.

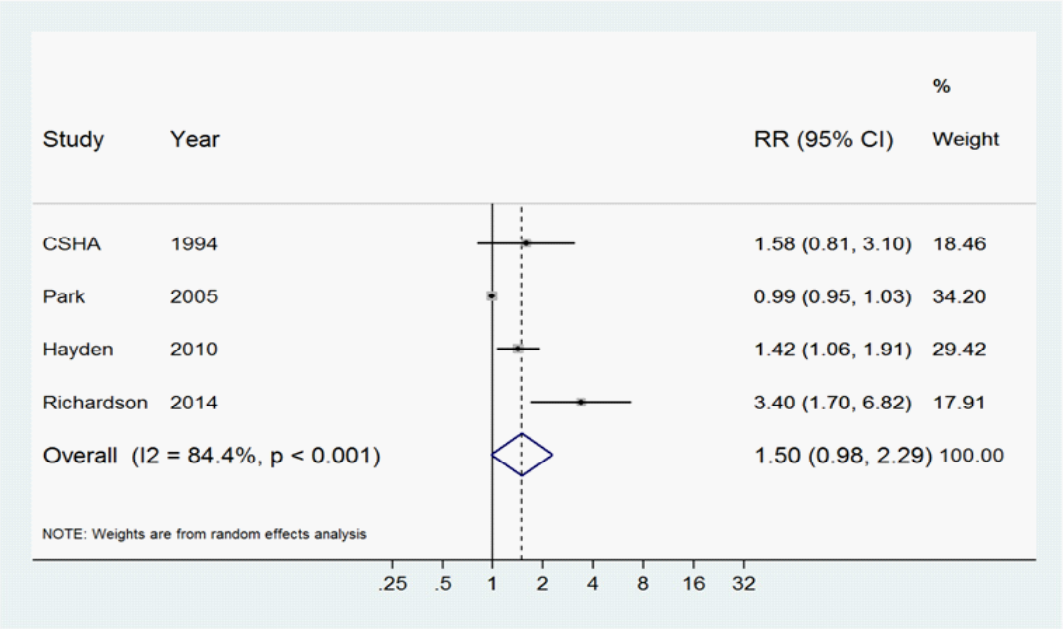

Figure 4: Forest plot for studies assessing the association between Alzheimer's disease and occupational exposure to pesticides. A random effect model was used. Heterogeneity was tested by the I^2 statistic, with $p<0.05$ indicating rejection of homogeneity.

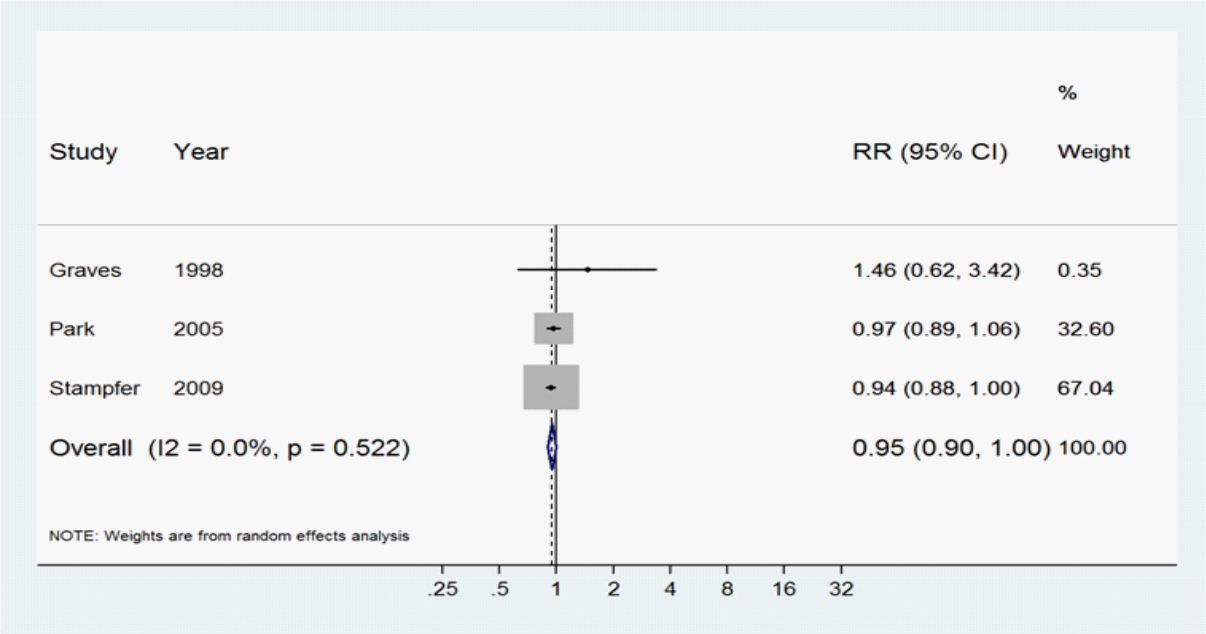

Figure 5: Forest plot for studies assessing the association between Alzheimer's disease and occupational exposure to metals. A random effect model was used. Heterogeneity was tested by the I^2 statistic, with $p<0.05$ indicating rejection of homogeneity

The risk estimates in the remaining ten studies were harmonized/inverted with low work complexity, low education and/or low job control as reference category **(Figure 6)**. The weighted risk estimate was 0.47 (95% CI: 0.35–0.63); after exclusion of an extreme outlier [18], this increased to 0.52 (95% CI: 0.40–0.68), and exclusion of the Canadian study [19] had a similar effect (RR: 0.52, 95% CI: 0.39–0.68). For cognitive work in particular the RR

increased from 0.46 to 0.72 (95% CI: 0.53 – 0.91) when Bickel [18] was excluded and the heterogeneity decreased to 27.6%. Overall, education had the highest impact, reducing the risk of Alzheimer's disease to one third while white versus blue collar works had the smallest impact on the risk. There were no clear indications of publication bias when the extreme outlier [18] was excluded, but the inclusion of this study influenced the test of publication bias towards significance.

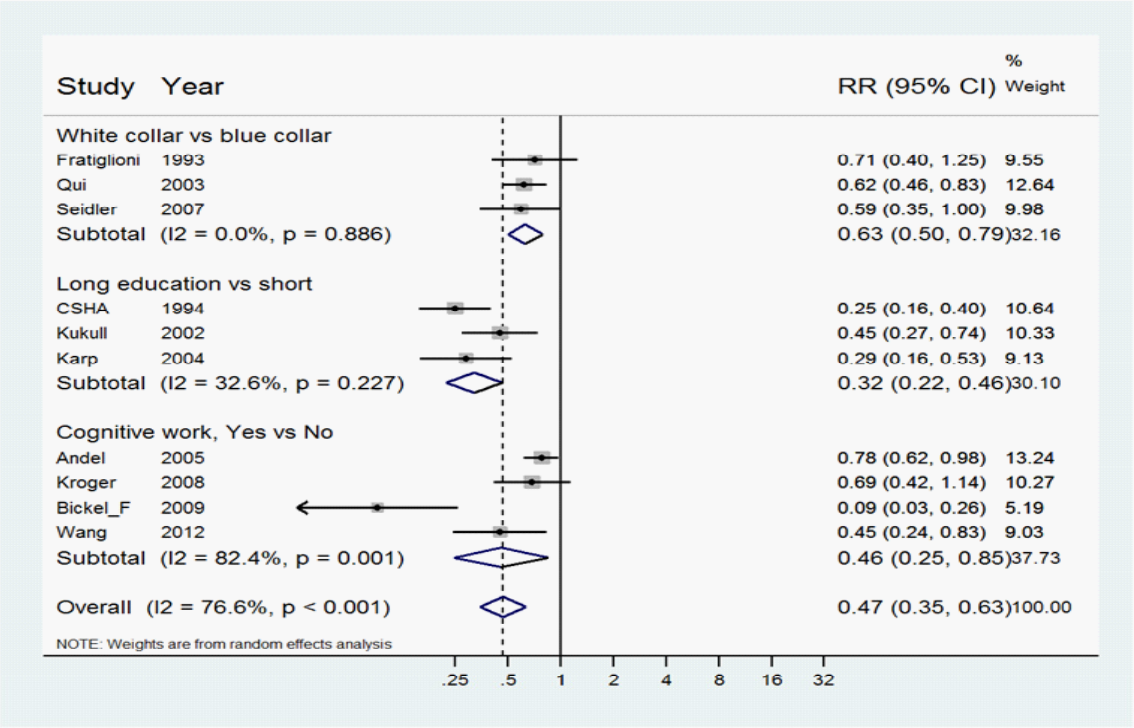

Figure 6: Forest plot for studies assessing the association between Alzheimer's disease and white-collar work versus blue-collar work, length of education, and cognitive demands at work. Results for women only are indicated by F; otherwise the results concern both sexes. Random effect models were used, with stratification for work and education. The heterogeneity was tested by the I^2 statistic, with $p<0.05$ indicating rejection of homogeneity.

4. Discussion

Weighted risk estimates based on scientifically high quality epidemiologic publications indicate that the risk of Alzheimer's disease is elevated after exposure to chemicals and possibly also after exposure to electromagnetic fields. The latter exposure might at least partially be explained by publication bias. However, the highest impact from occupation was related to a high degree of work complexity, which could reduce the risk of disease to less than half.

Meta-analyses have the general limitation that the calculations can only be based on published data and will reflect any inherent weaknesses of design in the studies included. Furthermore, all previously published meta-analyses of Alzheimer's disease have been based on all relevant publications identified, irrespective of the quality of the study design.

One strength of our study is that the meta-analyses were based on a systematic literature review including only studies fulfilling high scientific standards. In order to make a standardized examination of the publications we used an elaborated protocol [14] that was based on the

detailed check-list proposed by Armon. [13] For every publication the authors individually filled in the scores of the protocol and our inter-observer agreement was high; however if our scores were divergent, we rescrutinized the publication and found consensus. However, there is always room for a reader's own discretion when judging a publication. Before adapting our protocol we blindly tested it on articles graded in Armon [13] and also here we found very high agreement between our grading and that of Armon's quality assignment.

Another strength of our meta-analyses is that we focused heavily on finding all possible sources of bias, using stratification of data with regard to possible confounders such as study design, gender, and funding. We also looked for publication bias using both funnel plots and tests for publication bias.

Although much research in recent decades has focused on the role of the amyloid cascade in the degenerative processes of Alzheimer's disease, this hypothesis has failed to identify the mechanisms causing the neurodegenerative process. Another approach is to study the amyloid precursor protein (APP) from which the much smaller amyloid protein emanates. [72] APP is a transmembrane big protein that belongs to the group of 'housekeeping' proteins. Outside the cell, APP has several receptors for different external products, and the protein might be regarded as a 'lodge-keeper' transmitting information from the outside of the cell to the nucleus. Since APP is such a big molecule, the folding and turnover might be highly influenced by toxins such as pesticides as well as by ultra-fine particles. The latter exposure can come from combustion and smoking, and smoking almost doubles the risk of Alzheimer's disease [2].

Considering the available evidence, no biological pathways have been identified by which exposure to electromagnetic fields might precipitate pathological changes leading to Alzheimer's disease [9]. Publication bias and methodological shortcomings might explain the slightly elevated risk estimates found [8,73], a conclusion also supported by our meta-analyses. The funnel plot **(Figure 2)** showed that the risk estimates were not elevated in studies based on bigger study groups. The almost doubled risk caused by exposure to pesticides is of the same magnitude as that caused by exposure to tobacco smoking [2].

The highest protection against Alzheimer's disease was found for cognitive work and long education. The Bavarian School Sisters study, which included 442 female members of a religious order with an average of 54 years of membership of the order, had 60 participants diagnosed with Alzheimer's disease.[18] Those with longer education, with vocational training, and/or who had been appointed to leading positions were at much lower risk. Cognitive work can also be described in terms of work complexity, with regard to work with data, people, and things [74]. Two epidemiologic studies evaluating work complexity in relation to Alzheimer's disease [16,28] both found that the protective effect was most evident for complexity in relation to people, which can be seen as equivalent to having had leading positions in the

Bavarian School Sisters study [18]. The latter study also showed an evident protective effect of education.

There has been some discussion of whether the underlying protective effect is education, rather than work complexity per se. A twin study among 2 622 pairs of twins, including 146 individuals diagnosed with Alzheimer's disease [16], reported that the level of education was quite similar within each pair and would thus not convey bias in the analyses; the author concluded that education had its own protective effect independent of work complexity. Moreover, in the Bavarian School Sisters study, the protective effects of education, vocational training, and leading positions were additive and potentiated instead of linear [18].

Figure 7 provides a timeline illustrating the relationship between the protective factors. The individual starts with a certain degree of cerebral complexity predestined by their genes and early life experiences. The brain is then exposed first to education and later to cognitive tasks such as vocational training and work complexity, both of which factors increase the complexity of the neural network. In other words, exposure to challenging tasks improves the development of the brain. The factors are independent and have additive protective effects, although they are related; individuals who start with a high degree of cerebral complexity more frequently apply for higher education and those with higher education are more likely to work in leading positions and perform complex work.

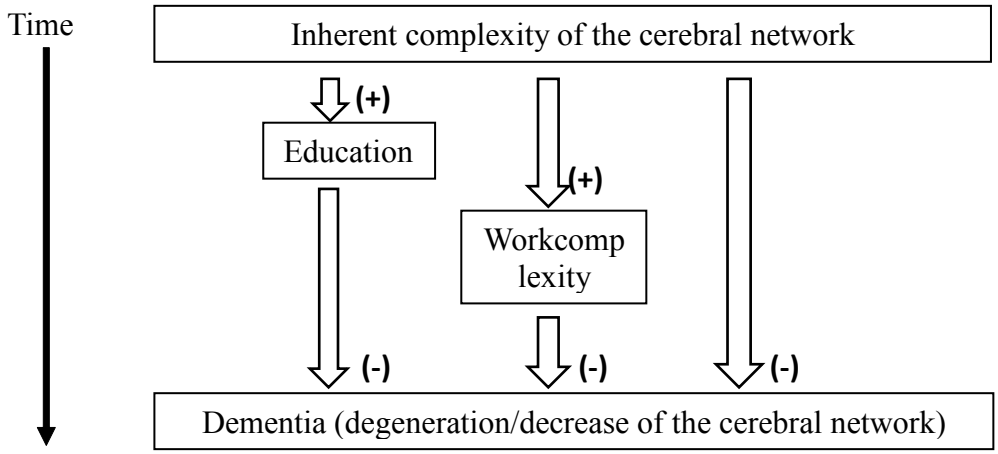

Figure 7: A graphical illustration of the interaction between different preventive factors and dementia. The arrow on the far left starts at birth and ends at death. The direction of each association is indicated within brackets, where (+) indicates a positive association (i.e. an enhanced ability to manage education and work complexity) and (-) indicates a negative association entailing an increased risk of development of dementia.

In a recent study, 323 middle-aged persons diagnosed with Alzheimer's disease underwent structural magnetic resonance imaging, cognitive evaluation, and work history assessment. [75] The results indicate that brain degeneration had a less harmful effect on cognition among those exposed to higher work complexity, although the brain atrophy was inexorably progressive. Thus, in people at risk of Alzheimer's disease, occupational complexity may confer resilience of cognition against progressive neurodegeneration. Additive protective effects can be expected

from inherent high brain complexity, further improved by the beneficial brain plasticity effects of a long education.

Table 1: Publications fulfilling good scientific standards (Armon class II or III) defined in an appendix (www.sjweh.fi/index.php?page=data-repository). [14] Diagnosis was graded at least score 3 (diagnosis from neurologist/psychiatrist, in-patient care or mortality register). The other categories involved at least a single score 2 or included in the interval 2-3 (1=Good, 2=Sufficient, 3=Uncertain/Insufficient).[EMF=electromagnetic fields, I=industry, PA=patient association, PU=public,?=funding is not possible to classify based on information in source text]

Publication	Year	Diagnosis	Exposure	Study group	Methods, analysis	Armon's global class [13]	Funding:	Exposures
Andel [16]	2005	1	1	2-3	1	III	PU	Occupation (work complexity)
Andel [17]	2010	1	1	2	1	II	PA, PU	Occupation (EMF)
Bickel [18]	2009	1	2	1	1	II	PU	Work complexity
CSHA [19]	1994	1	2	2	2	II	PU	Pesticides, chemicals, education
Feychting [20]	1998	1	1	2	1-2	II	PU	Occupation (EMF)
Feychting [21]	2003	3	2-3	1	1	III	PU	Occupation (EMF)
Fratiglioni [5]	1993	1	2	2-3	2	III	PU	Manual work
Graves [22]	1998	2	2	2-3	2-3	III	PU	Chemicals including metals
Graves [23]	1999	2	2	2-3	2-3	III	PU	Occupation (EMF)
Hakansson [24]	2003	3	2-3	2	1	III	I	Occupation (EMF)
Hayden [25]	2010	1	2	2-3	2	III	PU	Pesticides
Helmer [26]	2001	1	2-3	2-3	1	III	PU, I	Occupation (blue-collar work)
Karp [27]	2004	1	1	2-3	1	III	PU	Education
Kroger [28]	2008	1	2-3	2	1	III	PU	Work complexity
Kukull [29]	1995	1	2	2-3	1	III	PU	Solvents
Kukull [30]	2002	1	2	2-3	1	III	PU	Education
Noonan [31]	2002	3	2-3	2	1-2	III	?	Occupation (EMF)
Park [32]	2005	3	2-3	2	2	III	PU	Occupation (EMF, pesticides, metals, chemicals)
Qui [33]	2003	1	1	2-3	1	III	PA, PU	Occupation (blue-collar work)
Qui [34]	2004	1	1-2	2-3	1-2	III	PA, PU	Occupation (EMF)
Richardson [35]	2014	1	2	2-3	2	III	PU	Pesticides (DDT)
Roosli [36]	2007	3	1	2	2	III	PU	Occupation (EMF)
Savitz [37]	1998	3	2-3	2	2	III	I, ?	Occupation (EMF)

Savitz [38]	1998	3	2-3	2	2	III	?	Occupation (work with electricity)
Seidler [39]	2007	1	2	2-3	2	III	?	Occupation (EMF, blue-collar work)
Smyth [40]	2004	1	1	2-3	2	III	PU, I	Occupations (work complexity)
Sorahan [41]	2007	3	2	2	2	III	?	Power station workers
Sorahan [42]	2014	3	2	2	2	III	?	Power station workers (EMF)
Stampfer [43]	2009	3	2-3	2	2	III	I	Occupation (welding, metals)
Wang [44]	2012	1	1	2-3	1-2	III	PA, PU	Psychosocial stress (cognitive work)

Table 2: Publications not fulfilling good scientific standards (Armon global class IV or V) defined in an appendix (www.sjweh.fi/index.php?page=data-repository) [14]. The category Diagnosis was graded as 4 (dementia without separation of Alzheimer's disease) or any other category involved a single score 3 or 4 (3=Uncertain/Insufficient, 4=Unacceptable). [EMF=electromagnetic fields, I=industry, PA=patient association, PU=public,?=funding is not possible to classify based on information in source text]

Publication	year	Diagnosis	Exposure	Study group: selection, controls, missing data	Methods and analysis	Armon global class[13]	Funding:	Exposures
Amaducci [45]	1986	2	2-3	3-4	3	IV	PU	Possible risk factors
Baldi [46]	2003	2	2-3	3	1	IV	PU	Occupation (pesticides)
Beard [47]	1992	2-3	3-4	2-3	2	IV	PU	Medical journals (education)
Chandra [48]	1987	2	2-3	3	3	IV	?	Possible risk factors
Davanipour [49]	2007	1	2-3	3	2-3	IV	PU	Occupation (EMF)
French [50]	1985	2	3	3	3	IV	PU	Possible risk factors
Gauthier [51]	2001	2	2-3	3-4	2	IV	PU, I	Pesticides, chemicals and metals
Gun [52]	1997	2-3	3	3	2	IV	PU	Chemicals + vibrations
Harmanci [53]	2003	2	3	3	2-3	IV	I	Possible risk factors
Heyman [54]	1984	2-3	2	2-3	3	IV	PU	Animals
Johansen [55]	1998	4	2	2	2-3	V	PU, I	Occupation (EMF)

Johansen [56]	2000	4	2	2	2	V	PU, I	Occupation (EMF)
Lehman [57]	2012	4	1	2	3	V	PU	Professional American Football
Li [58]	1992	1	2-3	3-4	2-3	IV	?	Pesticides, chemicals and metals
O´Flynn [59]	1987	3	3	2	2-3	IV	?	Occupation (solvents)
Peters [60]	2013	3	3	2-3	2-3	IV	?	Company register (aluminum)
Ravaglia [61)	2002	1	2-3	3	2-3	IV	PU	Occupation (education, agricultural work)
Rovio (62)	2007	2	2	2-3	3	IV	PU	Physical activity
Salib (63)	1996	1	3	3	2	IV	?	Aluminum
Schulte (64)	1996	3	3	2-3	3-4	IV	PU	Occupation
Shalat (65)	1988	2	2	3	2-3	IV	PU	Occupation (lead, solvents)
Sobel (66)	1995	1	2	4	2-3	V	PU	Occupation (EMF)
Sobel (67)	1995	1-2	2-3	3-4	2-3	IV	PU	Occupation (EMF)
Tyas (68)	2001	1	2-3	3	2-3	IV	PU	Chemicals

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