The complex interaction of genetics and delirium: a systematic review and meta-analysis

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ABSTRACT

Objective: Understanding genetic predisposition to delirium. Methods: Following PRISMA guidelines, we undertook a systematic review of studies involving delirium and genetics in the databases of Pubmed, Scopus, Cochrane Library and PsycINFO, and performed a meta-analysis when appropriate. We evaluated 111 articles, of which 25 were finally included in the analysis. The studies were assessed by two independent researchers for methodological quality using the Downs and Black Tool and for genetic analysis quality. Results: We performed a meta-analysis of 10 studies of the *Apolipoprotein E* (APOE) gene, obtaining no association with the presence of delirium (LOR: 0.18, 95% CI: − 0.10-0.47, p = 0.21). Notably, only 5 out of 25 articles met established criteria for genetic studies (good quality) and 6 were of moderate quality. Seven studies found an association with APOE4, the dopamine transporter gene SCL6A3, dopamine receptor 2 gene, glucocorticoid receptor, melatonin receptor and mitochondrial DNA haplotypes. One genome-wide association study found two suggestive long intergenic non-coding RNA genes. Five studies found no association with catechol-o-methyltransferase, melatonin receptor or several interleukins genes. The studies were heterogenous in establishing the presence of delirium. Conclusions: Future studies with large samples should further specify the

delirium phenotype and deepen our understanding of interactions between genes and other biological factors.

Keywords: Delirium, Dementia, Genetics, Biomarkers, Systematic Review.

INTRODUCTION

Delirium is a common complex neuropsychiatric disorder that is common across clinical settings, affecting approximately a third of hospitalised patients [1], with higher rates in those with pre-existing dementia and/or receiving care in palliative or intensive care settings [2]. Delirium is associated with a variety of adverse outcomes that include a higher risk of mortality, institutionalisation, increased length of hospital stay and dementia [3,4].

Although the underlying causes can vary greatly, delirium has a relatively consistent clinical presentation that includes a number of core symptom domains: cognitive (attention, visuospatial ability, orientation, and memory), higher order thinking (language, thought process, and executive function), and circadian (sleep-wake cycle and motor activity). Inattention is the cardinal cognitive feature as it is consistently and disproportionately affected. In addition,

delirium can include a variety of non-core symptoms such as affective and psychotic [5].

This convergence of different aetiologies into a common clinical manifestation has led to the hypothesis of a common pathophysiological pathway that is relatively independent of the original insult, where different neurotransmitters and neuronal networks may be involved [6,7]. However, the specific physiological changes that underlie the delirium clinical presentation are incompletely understood, including genetic factors that might be involved in this process.

Delirium genetics have been subject to limited study to date, with existing studies indicating conflicting results. One systematic review in 2009 considered all possible genes associated with delirium (both due to a medical cause and substance-induced delirium), and found that delirium due to a medical cause was mostly related to the apolipoprotein E (APOE) gene and in only one case to another candidate gene (SOAT1) [8]. The APOE gene is the most studied gene in delirium in the elderly, due to its demonstrated relation to dementia, a known risk factor for delirium [9] and with which it shares some critical symptoms.

Although studies have yielded conflicting results, two meta-analyses published in 2009 and 2016 [10,11] found no association of this gene with delirium.

Since the publication of these reviews, other work has been published that explores the genetics of delirium due to medical cause. Our objective was to conduct a systematic review of these new studies, and perform a meta-analysis if appropriate.

METHODS

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) guidelines [12]. We searched in the databases Pubmed, Scopus, Cochrane Library and PsycINFO, using the following keywords: ("delirium" OR "acute confusional state" OR "acute confusion") AND ("genotype" OR "polymorphism" OR "gene*"OR "Polymorphism, Genetic" OR "Amplified Fragment Length Polymorphism Analysis" OR "Polymorphism, Single Nucleotide" OR "Polymorphism, Single-Stranded Conformational" OR "Polymorphism, Restriction Fragment Length" OR "DNA Copy Number

Variations") . The final search was done on November 3rd of 2019 and we did not limit for language, year of publication or age. We also searched for other relevant articles in the references of original papers and reviews.

Study selection

Two authors (DA, ES) independently performed the screening of the title and abstract of all articles yielded by the keywords search and then, also independently, reviewed the full-text articles of the selected studies. Any disagreement between them was resolved by consensus. Studies were included if: a) clearly defined delirium and non-delirium groups were compared by using a validated scale or research diagnostic criteria, b) data were available for the meta-analysis from the paper or the authors provided raw data upon request, and c) duplicated studies were included only once (using the paper with the higher number of participants). For the meta-analysis only prospective studies were included. Studies that focused upon substance-induced delirium/delirium tremens were excluded. Studies based on RNA were also excluded.

Assessment of general methodological quality

The studies were assessed for methodological quality using the Downs and Black Tool[13], which examines methodological strengths and weaknesses of both randomised and non-randomised studies for systematic reviews [14].The tool includes a checklist of 27 items (total score ranging from 0 – 31) distributed between 5 subscales: Reporting (10 items 11 points); External Validity (3 items); Bias (7 Items); Confounding (6 Items) and Power (1 Item: 5 points). Higher scores indicate better methodological quality. The suggested cut-off points to categorise study quality are excellent (>26); good (20-25); fair (15-19) and poor (≤14)[15,16]. The DBT (Downs and Black Tool) has been demonstrated to have good validity, internal consistency (KR-20=0.89), test retest reliability (r=0.88) and inter-rater reliability (r=0.75)[13,14]. Given that power is not a property of a quality assessment and because it is a difficult item to calculate, we use the modification of Trac et al [17] where a score of 0 was assigned if no power calculation was reported and 1 if there was a power calculation irrespectively of whether the power was adequate or not. Thus, in this modified checklist the maximum score is 28.

The DBT scoring was performed independently (blind) by two of the research team (ES and DM). Any differences between the two raters in each domain

were resolved through a review by a third researcher (DA) who allocated the final score. We evaluated the methodological quality of only those articles that were selected for the meta-analysis.

Assessment of genetic analysis quality

Many published candidate gene case-control studies failed to be replicated because of the presence of methodological limitations. Two researchers (EV and SA) independently checked each selected study to score them according to the following requirements for this type of study [18,19]:

1. Sample size and case:control ratio
2. Accuracy of genotyping and calling rate
3. Accomplishment of the Hardy Weinberg equilibrium in each genetic variant
4. No presence of sample stratification
5. Unrelatedness of study subjects
6. Correction for multiple testing (if appropriated)
7. Results were replicated in an independent sample

We scored the selected studies using the above-mentioned items. Accordingly, articles were considered to be of good quality if they scored ≥5 and of moderate quality with a score of 4. Studies with scores below 4 were considered to be of low quality.

Statistical analysis

For the meta-analysis, given that the studies included different populations, a random-effects model was incorporated, which allows inference on the average effect in the entire population of studies from which the included studies are assumed to be a random selection.

For the measurement of effect size, the log odds ratio (LOR) was calculated using restricted maximum likelihood estimation. In addition, homogeneity was investigated using the Q test and for the quantification of heterogeneity, the Higgins' I2 (which shows the percentages of variance not explained by chance) was calculated. We explored bias in study availability (publication bias) by visual inspection of funnel plot and using Egger's test. Analysis was carried out with the 'metafor' package of R software[20].

If a study reported median and interquartile range for some variable, we calculated the mean and standard deviation based on a described algorithm [21].

RESULTS

After elimination of duplicates and review of abstracts, we obtained 111 full-text articles which were evaluated thoroughly. Of these, 86 were excluded due to being review rather than original papers (n=10), focusing exclusively on delirium tremens (n=63), using RNA instead of DNA (n=2), having the sample included in another article (n=5), not defining delirium vs. non-delirium groups (n=4) or not using any scale/research diagnostic criteria (n=2) (see Online Resources 1-6). Ultimately, we included 25 studies in the analysis (see Figure 1 for the PRISMA flow chart and Online Resource 7 for the PRISMA checklist)

General characteristics of the studies included

Most studies used screening scales to define the presence of delirium, mainly the Confusion Assessment Method or its adaptation for the Intensive Care Unit (CAM/CAM-ICU). Others used the Intensive Care Delirium Screening Checklist (ICDSC), while only a small number of articles used DSM or ICD criteria, alone or in combination with a screening tool. Diagnosis was made mainly prospectively, with the exception of two studies with retrospective design [22,23] and another where some of its sample was analysed retrospectively [24] (see Table 1). The number of times that patients were screened for delirium was very heterogeneous, some patients were evaluated once, others every 8 hours, some of them daily or in specific days for a period of time and others until discharge (data not shown). Not all studies defined the genetic population, of those that did one was based on an European-ancestry population [22], two on a sample with less than 10% of non-white population [25,26] and one on a sample with 16% of African Americans [23]. Eight articles did not define the patient's dementia status [23,27–33].

The selected studies are presented in groups according the gene system involved or type of study. The final rating of genetic quality is reported for each study in Table 1, detailed scores are shown in the Online Resource 8.

Only APOE studies were suitable for meta-analysis. For the COMT gene we obtained three articles with inadequate numbers to perform a robust meta-analysis.

Studies in APOE and delirium

Eleven studies of APOE met the inclusion criteria (Table 1). Most studies did not find an association between APOE and delirium emergence [25,27,28,34–39]. Leung et al[30] found a higher risk of delirium after non-cardiac surgery in patients with at least one ε4 allele and after adjusting for other variables (OR: 3.64; 95% CI: 1.51–8.77). However, this study was rated to have low quality in terms of a case-control genetic analysis. Likewise, van Munster et al[10] found a similar positive association in a mixed sample of medical and surgical patients, also after adjusting for other variables (OR: 1.7, 95%CI: 1.1-2.6, p= 0.022). Notably, this study was scored as having moderate genetic analysis quality. Although some of the above mentioned authors found no association with the occurrence of delirium, they did find an association between having one ε4 allele and suffering a longer episode of delirium [27,34] or, conversely in one study, with a shorter duration of the episode and also lower mortality [38]. Also, one study found that a model including female gender, lower levels of the

insulin-like growth factor-I (IGF-I) and absence of the APOE epsilon 4 allele predicted 77.8% of recoveries and 75% of non-recoverers from delirium during the hospitalisation[34]. However, all these studies were rated as low genetic analysis quality.

Meta-analysis of studies in APOE and delirium

Ten studies were selected for meta-analysis (see Table 2 for a summary of their data). The study of Ely et al[27] was excluded, as they did not provide data for the estimation of the effect sizes. The methodological quality of the included studies is shown in Online Resource 9, four studies were of good quality[10,30,35,39] and 6 of fair quality[25,28,34,36–38].

The meta-analysis included data for 2589 participants of whom 1256 (48.5%) were males and 479 (18.5%) were diagnosed with delirium by systematic methods. Six hundred and thirteen (n=613, 23.7%) of the participants had at least one copy of the APOE ε4 allele. The total numbers of each subsample were: n= 174 with delirium and at least one copy of APOE ε4 allele, n= 439 without delirium and carriers of APOE ε4 allele, n= 476 with delirium but no

carriers of APOE ε4 allele, and n=1500 without delirium and without any copy of APOE ε4 allele. (See also table 1).

Using a random-effects model with restricted maximum likelihood estimation, it was found that the possession of the APOE ε4 allele has a small (LOR: 0.18, 95% CI: − 0.10-0.47), nonsignificant (p = 0.21) effect on the presence or not of delirium. The forest plot for the meta-analysis of the studies is shown in Figure 2.

The Q test for heterogeneity showed no significant heterogeneity among the studies Q= 14.32, df:9, p= 0.11 and the I^2= 28.86%, which indicates a moderate heterogeneity, although not significant.

We assessed publication bias using Funnel plot (figure 3) and regression test for funnel plot asymmetry showed no evidence of funnel plot asymmetry (t = -1.60, df = 8, p = 0.15) and therefore no publication / availability bias.

Studies involving the neurotransmission process and delirium

Studies are summarized in Table 1. Van Munster et al.[40] investigated the association of delirium with a large number of polymorphisms (thirty-two) in genes related to dopamine: the dopamine receptor 2 (DRD2), the dopamine receptor 3 (DRD3) and the dopamine transporter (SLC6A3) genes. They found after a multivariable logistic regression model including other significant variables, that three SNPs were associated with lower risk of delirium, two in the SLC6A3 gene: rs393795 (OR: 0.20, 95% CI: 0.06–0.63, P= 0.004) and rs1042098 (OR: 0.55, 95%CI 0.35–0.88, P= 0.036) and one of the DRD2 gene: rs6276 (OR:0.29, 95%CI: 0.14–0.59, P= 0.002), this analysis was performed following the requirements for case-control genetic analysis (scored with high quality). The same team in a later work [24] combined their sample with other five European samples (which were not previously evaluated for these genes) in order to analyse the three polymorphisms found to be protective, and reported that the homozygous AA genotype of the SNP rs393795 in the SLC6A3 gene was more frequent in patients without delirium in all the individually available populations as well as in the meta-analysis of all the samples (OR: 0.37, 95%CI: 0.21–0.63, P= 0.0003) and that the homozygous GG genotype of rs6276 in the dopamine receptor 2 (DRD2) gene had a trend to be more frequent in patients without delirium and with cognitive impairment (95% C.I. 0.4–1.0, P=0.06).

Catechol-O-methyltransferase (COMT) gene polymorphisms have been investigated in three studies. In the first work that we rated with high genetic quality analysis score, Van Munster et al.[41] found that none of three polymorphisms studied (rs4680, rs6269, rs4818) were individually related to delirium but the haplotype AGG decreased its risk (OR: 0.67, 95% CI: 0.49–0.93, p =0.02) after adjustment for pre-existing cognitive impairment. The other two works investigated only the SNP rs4680, had medium and lower genetic quality analysis scores and reported conflicting results: Vasunilashorn et al.[26] found that the genotype (VAL/VAL) was not directly related to delirium but protected against an increased risk of delirium in patients for elective major surgery with high postoperative C-reactive protein (CRP) levels, and Nekrosius et al.[32] described this same genotype to increase the risk of delirium (OR:4.57, 95% CI:1.11-18.9, P=0.036) in a young population of patients with traumatic brain injury.

Finally, Kazmierski[42] investigated a possible relationship between delirium and SNPs in the N-methyl-D-aspartate (NMDA) receptor 3A (GRIN3A) and in the 2B (GRIN2B) subunits genes and the serotonin 2A (HTR2A) receptor gene and found that the 3723G/A (rs3739722) GRIN3A gene was associated with an

increased risk of postoperative delirium (OR: 45.84, 95% CI. 1.23–1706.21, P=0.038) and also with lower baseline Montreal Cognitive Assessment (MoCA) score and longer duration of delirium. The study was conducted in a very small sample size (32 patients and 32 controls) and without other quality control requirements, therefore the results cannot be considered conclusive.

Studies in other genes and delirium.

Studies have addressed for possible relationships between a variety of other genes (sterol O-acyltransferase 1, Interleukin-6, Interleukin-6 Receptor, Interleukin-8, melatonin receptor 1B, CYP305, P-glycoprotein, breast cancer-related protein) and delirium (see Table 1) with no significant results [29,31,43,44]. Mahanna-Gabrielli et al. [22] found the homozygous GG genotype of rs10830963 of the melatonin receptor 1b gene increased the incidence of postoperative delirium in a small group of cardiac surgery patients (OR: 5.2, 95% CI 1.0-26.1, P=0.05). Manenschijn et al.[45] studied the association of delirium with six possible haplotypes resulting from six SNPs of the glucocorticoid receptor gene (NR3C1) and found that homozygous carriers of the *Bcl*I-*TthIII*I haplotype, after adjusting for age and functional and cognitive

impairment, had a lower risk for delirium (OR: 0.081. 95% CI: 0.009–0.710, P=0.023).

Only one study investigated the association of delirium with mitochondrial DNA[23] and found that after adjusting for age, the haplogroup clade IWX was associated to delirium (OR:1.36; 95% CI: 1.13-1.64, p: 0.001) in Caucasians and the haplogroup L3 was protective for delirium (OR. 0.60; 95% CI: 0.38-0.94; p: 0.03) in African Americans.

Genome-wide association (GWAS) studies and delirium

A GWAS study[33] evaluated delirium among four other possible complications that can occur after cardiac surgery and did not found any SNP associated with delirium with genome-wide significance ($p < 5 \times 10^{-8}$) but did find a promising association ($p < 1 \times 10^{-5}$) with two long intergenic non-coding RNA genes: AC074391.1 /rs13008718 and LINC00871 (Long intergenic non-protein coding RNA 871/ rs188623516).

DISCUSSION

In this review only a few articles found single genes that were associated with the presence of delirium and passed the evaluation for quality control for genetic studies: one study found association of delirium with the possession of the APOE ε4 allele[10], two studies reported the dopamine transporter SLC6A3 (rs393795) to reduce delirium risk (with a positive trend also for the SNP rs6276 in the dopamine receptor 2 -DRD2-)[24,40] and another reported a suggestive role of rs10830963 SNP of melatonin receptor 1B in the development of postoperative delirium [22]. It is important to highlight that methodologically well performed studies discarded the association between COMT [26,41], MTNR1B (melatonin receptor)[44] and ILs (Interleukin-6, Interleukin-6 Receptor and Interleukin-8)[43] genes with delirium and another found that a specific haplotype of the NR3C1 (glucocorticoid receptor)[45] was associated with lower risk of delirium. We could only perform a meta-analysis for the APOE gene and found no association with delirium, in line with previous meta-analysis[10,11].

On the other hand, some studies have found association between a number of genes with characteristics of delirium such as longer episode duration in patients with the APOE-ε4 allele[27,34] and the SNP rs3739722 in the NMDA

receptor GRIN3A[42], a more severe episode in carriers of the APOE-ε4 allele [46], but also a shorter duration of the episode and lower mortality (in a younger and smaller sample) in delirium patients with the APOE-ε4 allele[38]. Other work reported no relationship between APOE-ε4 and severity of delirium in an elderly inpatient sample[47]. However, most of these studies have important methodological limitations.

With a novel approximation, one study found a mitochondrial haplogroup (IWX)[23] associated with higher risk of delirium in Caucasians and another (L3) protective for delirium in African Americans, probably the first involving the this oxidative stress pathway in delirium[7], which has been described in neurodegenerative diseases[48].

Genomic-Wide Association Studies (GWAS) have emerged as helpful approaches to complex diseases that can identify individual or groups of genes beyond the limits of single-gene association studies, confirming previous research and opening up new perspectives. Only one GWAS was included in our review [33], which did not find any gene with genome-wide significance. However, they found two suggestive SNPs located in two long intergenic non-coding RNA genes. Note that we did not include a second GWAS study in our

analysis because they did not use a validated scale or research diagnostic criteria, among other methodological flaws[49].

Some studies have found no single SNPs associated to delirium, but have found associations to specific haplotypes (of COMT and the NR3C1 glucocorticoid receptor)[41,45]. Also, genes may not have a direct effect on delirium but may impact through other factors, as for example the VAL/VAL genotype of the COMT gene appears protective in terms of the risk of delirium linked to higher levels of the proinflammatory factor CRP[26]. In another recent study, the APOE-ε4 allele was found to be associated with an increased risk of delirium and severity of delirium episode in patients with high CRP levels [50]. Lower levels of IGF-I in association with absence of the APOE-ε4 allele and female gender predicted a higher probability of recovery from delirium [34] and with similar IGF-I levels, patients with at least one APOE-ε4 allele were more likely to cognitively improve, independent of the presence of delirium [51].

Discrepancies in genetic studies could arise from phenotypes not correctly defined. Different diagnostic criteria and screening scales in delirium have low agreement [52,53] and the studies in our review used a different range of methods to diagnose delirium, frequently applying screening scales. We

excluded two large studies for not using any validated scale or research criteria (one GWAS [49] and one about APOE [54]) which would have otherwise provided valuable genetic information. Also, delirium status was determined in different times of the clinical process, which could have resulted in some patients being incorrectly identified.

Most of the studies in our review examined candidate genes because of their suspected connection to pathways leading to common symptoms in delirium (e.g. psychosis, cognitive disturbances, sleep/wake cycle, etc.) and/or their association in other studies with diseases with symptoms shared with delirium, predominantly dementia but also depression and schizophrenia, among others. Although a gene or group of genes could be associated with the entire clinical manifestation of delirium, that genetic association may be with specific delirium subtypes (e.g. motor)[55] or to particular symptoms or symptom clusters, such as the core symptoms (circadian, cognitive and higher order thinking)[5] in full syndromal or subsyndromal delirium [56]. Also, genes may confer brain vulnerability to certain etiological insults but not to others. These, among other possible underlying neurophysiological pathways [57] have not been addressed in studies.

Future studies should include more precisely defined delirium, its clinical subtypes and also dementia status. Given the strong association between some genes and dementia, particularly (but not exlusively) APOE ε4, all delirium genetic studies should use dementia as a covariate or as a stratifying variable when defining the sample. Also, bigger samples would be needed in order to obtain more reliable results on genes already studied (e.g. APOE or COMT) or new approximations, based on the phenomenology of delirium, pathophysiological substrates or new GWAS studies, where interactions between genes and to other biological factors can be considered more fully and enhance our understanding of the complex mechanisms that underpin the emergence of the syndrome.

In conclusion, our systematic review included a number of recent studies of a variety of genes that may be linked with delirium and found few positive associations. Only one gene, the APOE, had sufficient data to allow for a meta-analysis which indicated negative results. New interesting insights have emerged about the possible relationship of genes with other genes but also with proinflammatory, neuroprotective or hormonal factors which may help us to understand the complex mechanisms of how genetic factors modify the risk of having delirium in certain circumstances. The scarcity of studies, many using

small samples, and absence of homogenous delirium phenotype definition indicates a need for further research. Both candidate gene studies and GWAS studies with large samples and gold standard methods are needed to elucidate if delirium has a genetic basis and if so, which genetic variants are involved.

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Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Ethics approval

The manuscript does not contain clinical studies or patient data.

Consent to participate

The manuscript does not contain clinical studies or patient data.

Consent for publication

Not applicable

Availability of data and material

All data generated or analysed during this study is included within this article (and its supplementary information files).

Code availability

Not applicable

Authors' contributions

Esteban Sepulveda and Elisabet Vilella developed the article's concept, Esteban Sepulveda and Dimitrios Adamis performed the article search, Esteban Sepulveda, Dimitrios Adamis and David Meagher performed the methodological quality analysis, Elisabet Vilella and Selena Aranda performed the genetic quality analysis, Dimitrios Adamis performed the meta-analysis, Esteban Sepulveda and Dimitrios Adamis wrote a first draft of the manuscript, all authors critically revised the work and all authors read and approved the final manuscript.

Fig. 1 Flow diagram of the study

Fig. 2 Forest Plot: association of delirium and APOE ε4 possession

Fig. 3 Funnel plot

Bibliography

1. Ryan DJ, O'Regan NA, Caoimh RO, Clare J, O'Connor M, Leonard M, et al. Delirium in an adult acute hospital population: predictors, prevalence and detection. BMJ Open. 2013;3:e001772.

2. Kalish VB, Gillham JE, Unwin BK. Delirium in older persons: evaluation and management. Am Fam Physician. 2014;90:150–8.

3. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA. Department of Geriatric Medicine, Medical Center Alkmaar, Alkmaar, The Netherlands.; 2010;304:443–51.

4. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006;35:350–64.

5. Sepulveda E, Franco JG, Trzepacz PT, Gaviria AM, Meagher DJ, Palma J, et al. Delirium diagnosis defined by cluster analysis of symptoms versus diagnosis by DSM and ICD criteria: diagnostic accuracy study. BMC Psychiatry. 2016;16:167.

6. Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. Semin Clin Neuropsychiatry. 2000;5:132–48.

7. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. Int J Geriatr Psychiatry. 2018;33:1428–57.

8. Adamis D, Van Munster BC, Macdonald AJD. The genetics of deliria. Int Rev Psychiatry. England; 2009;21:20–9.

9. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet. Elsevier Ltd; 2014;383:911–22.

10. van Munster BC, Korevaar JC, Zwinderman AH, Leeflang MM, de Rooij SEJA. The association between delirium and the apolipoprotein E epsilon 4 allele: new study results and a meta-analysis. Am J Geriatr Psychiatry. England; 2009;17:856–62.

11. Adamis D, Meagher D, Williams J, Mulligan O, McCarthy G. A systematic review and meta-analysis of the association between the apolipoprotein E genotype and delirium. Psychiatr Genet. 2016;26:53–9.

12. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6:e1000097.

13. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. BMJ Publishing Group; 1998;52:377–84.

14. Hootman JM, Driban JB, Sitler MR, Harris KP, Cattano NM. Reliability and validity of three quality rating instruments for systematic reviews of observational studies. Res Synth Methods. Wiley; 2011;2:110–8.

15. Hooper P, Jutai JW, Strong G, Russell-Minda E. Age-related macular degeneration and low-vision rehabilitation: a systematic review. Can J Ophthalmol. 2008;43:180–7.

16. Silverman SR, Schertz LA, Yuen HK, Lowman JD, Bickel CS. Systematic review of the methodological quality and outcome measures utilized in exercise interventions for adults with spinal cord injury. Spinal Cord. 2012. p. 718–27.

17. Trac MH, McArthur E, Jandoc R, Dixon SN, Nash DM, Hackam DG, et al. Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. CMAJ. Canadian Medical Association; 2016;188:e120–9.

18. Jorgensen TJ, Ruczinski I, Kessing B, Smith MW, Shugart YY, Alberg AJ. Hypothesis-driven candidate gene association studies: Practical design and analytical considerations. Am J Epidemiol. Am J Epidemiol; 2009;170:986–93.

19. Hong EP, Park JW. Sample Size and Statistical Power Calculation in Genetic Association Studies. Genomics Inform. Korea Genome Organization; 2012;10:117.

20. Viechtbauer W. Conducting meta-analyses in R with the metafor. J Stat Softw. 2010;36:1–48.

21. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.

22. Mahanna-Gabrielli E, Miano TA, Augoustides JG, Kim C, Bavaria JE, Kofke WA. Does the melatonin receptor 1B gene polymorphism have a role in postoperative delirium? PLoS One. United States; 2018;13:e0207941.

23. Samuels DC, Hulgan T, Fessel JP, Billings FT, Thompson JL, Chandrasekhar R, et al. Mitochondrial DNA Haplogroups and Delirium During Sepsis. Crit Care Med. 2019;47:1065–71.

24. van Munster BC, de Rooij SEJA, Yazdanpanah M, Tienari PJ, Pitkala KH, Osse RJ, et al. The association of the dopamine transporter gene and the dopamine receptor 2 gene with delirium, a meta-analysis. Am J Med Genet B Neuropsychiatr Genet. United States; 2010;153B:648–55.

25. Vasunilashorn SM, Ngo L, Kosar CM, Fong TG, Jones RN, Inouye SK, et al. Does Apolipoprotein E Genotype Increase Risk of Postoperative Delirium? Am J Geriatr Psychiatry. Division of General Medicine and Primary Care, Department of Medicine, Beth Israel Deaconess Medical Center, Office 212, 1309 Beacon St., Boston, MA 02446, United States; 2015;23:1029–37.

26. Vasunilashorn SM, Ngo LH, Jones RN, Inouye SK, Hall KT, Gallagher J, et al. The Association Between C-Reactive Protein and Postoperative Delirium

Differs by Catechol-O-Methyltransferase Genotype. Am J Geriatr Psychiatry. England; 2019;27:1–8.

27. Ely EW, Girard TD, Shintani AK, Jackson JC, Gordon SM, Thomason JWW, et al. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. Crit Care Med. United States; 2007;35:112–7.

28. Tagarakis GI, Tsolaki-Tagaraki F, Tsolaki M, Diegeler A, Tsilimingas NB, Papassotiropoulos A. The role of apolipoprotein E in cognitive decline and delirium after bypass heart operations. Am J Alzheimers Dis Other Demen. United States; 2007;22:223–8.

29. Tagarakis GI, Tsolaki-Tagaraki F, Tsolaki M, Diegeler A, Kazis D, Rouska E, et al. The role of SOAT-1 polymorphisms in cognitive decline and delirium after bypass heart surgery. Clin Res Cardiol. Germany; 2007;96:600–3.

30. Leung JM, Sands LP, Wang Y, Poon A, Kwok P, Kane JP, et al. Apolipoprotein E e4 allele increases the risk of early postoperative delirium in older patients undergoing noncardiac surgery. Anesthesiology. United States; 2007;107:406–11.

31. Skrobik Y, Leger C, Cossette M, Michaud V, Turgeon J. Factors predisposing to coma and delirium: fentanyl and midazolam exposure; CYP3A5, ABCB1, and ABCG2 genetic polymorphisms; and inflammatory factors. Crit Care Med. United States; 2013;41:999–1008.

32. Nekrosius D, Kaminskaite M, Jokubka R, Pranckeviciene A, Lideikis K, Tamasauskas A, et al. Association of COMT Val158Met Polymorphism With Delirium Risk and Outcomes After Traumatic Brain Injury. J Neuropsychiatry Clin Neurosci. 2019;31:298–305.

33. Westphal S, Stoppe C, Gruenewald M, Bein B, Renner J, Cremer J, et al. Genome-wide association study of myocardial infarction, atrial fibrillation, acute stroke, acute kidney injury and delirium after cardiac surgery - A sub-analysis of the RIPHeart-Study. BMC Cardiovasc Disord. 2019;19.

34. Adamis D, Treloar A, Martin FC, Gregson N, Hamilton G, Macdonald AJD. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. Int J Geriatr Psychiatry. England; 2007;22:688–94.

35. Bryson GL, Wyand A, Wozny D, Rees L, Taljaard M, Nathan H. A prospective cohort study evaluating associations among delirium, postoperative cognitive dysfunction, and apolipoprotein E genotype following open aortic repair. Can J Anaesth. United States; 2011;58:246–55.

36. Abelha FJ, Fernandes V, Botelho M, Santos P, Santos A, Machado JC, et al. Apolipoprotein E e4 allele does not increase the risk of early postoperative delirium after major surgery. J Anesth. Japan; 2012;

37. Oldenbeuving AW, de Kort PLM, Kappelle LJ, van Duijn CM, Roks G. Delirium in the acute phase after stroke and the role of the apolipoprotein E

gene. Am J Geriatr Psychiatry. England; 2013;21:935–7.

38. Alexander SA, Ren D, Gunn SR, Kochanek PM, Tate J, Ikonomovic M, et al. Interleukin 6 and apolipoprotein E as predictors of acute brain dysfunction and survival in critical care patients. Am J Crit Care. United States; 2014;23:49–57.

39. Cunningham EL, Mawhinney T, Beverland D, O'Brien S, McAuley DF, Cairns R, et al. Observational cohort study examining apolipoprotein E status and preoperative neuropsychological performance as predictors of post-operative delirium in an older elective arthroplasty population. Age Ageing. England; 2017;46:779–86.

40. van Munster BC, Yazdanpanah M, Tanck MWT, de Rooij SEJA, van de Giessen E, Sijbrands EJG, et al. Genetic polymorphisms in the DRD2, DRD3, and SLC6A3 gene in elderly patients with delirium. Am J Med Genet B Neuropsychiatr Genet. United States; 2010;153B:38–45.

41. van Munster BC, Baas F, Tanck MW, de Rooij SEJA. Polymorphisms in the catechol-o-methyltransferase gene and delirium in the elderly. Dement Geriatr Cogn Disord. Switzerland; 2011;31:358–62.

42. Kazmierski J, Sieruta M, Banys A, Jaszewski R, Sobow T, Liberski P, et al. The assessment of the T102C polymorphism of the 5HT2a receptor gene, 3723G/A polymorphism of the NMDA receptor 3A subunit gene (GRIN3A) and 421C/A polymorphism of the NMDA receptor 2B subunit gene (GRIN2B) among

cardiac surgery patients with and without d. Gen Hosp Psychiatry. United States; 2014;36:753–6.

43. van Munster BC, Zwinderman AH, de Rooij SE. Genetic variations in the interleukin-6 and interleukin-8 genes and the interleukin-6 receptor gene in delirium. Rejuvenation Res. United States; 2011;14:425–8.

44. de Jonghe A, de Rooij S, Tanck MWT, Sijbrands EJG, van Munster BC V. Polymorphisms in the melatonin receptor 1B gene and the risk of delirium. Dement Geriatr Cogn Disord. Switzerland; 2012;33:306–10.

45. Manenschijn L, van Rossum EF, Jetten AM, de Rooij SE, van Munster BC. Glucocorticoid receptor haplotype is associated with a decreased risk of delirium in the elderly. Am J Med Genet B, Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet. Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands. l.manenschijn@erasmusmc.nl: Wiley-Liss, Inc; 2011;156B:316–21.

46. Massimo L, Munoz E, Hill N, Mogle J, Mulhall P, McMillan CT, et al. Genetic and environmental factors associated with delirium severity in older adults with dementia. Int J Geriatr Psychiatry. England; 2017;32:574–81.

47. Adamis D, Lunn M, Martin FC, Treloar A, Gregson N, Hamilton G, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. Age Ageing. England; 2009;38:326–32; discussion 251.

48. Area-Gomez E, Guardia-Laguarta C, Schon EA, Przedborski S. Mitochondria, OxPhos, and neurodegeneration: Cells are not just running out of gas. J. Clin. Invest. 2019.

49. McCoy Jr. TH, Hart K, Pellegrini A, Perlis RH, McCoy THJ, Hart K, et al. Genome-wide association identifies a novel locus for delirium risk. Neurobiol Aging. Center for Quantitative Health, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, United States, United States; 2018;68:160.e9-160.e14.

50. Vasunilashorn SM, Ngo LH, Inouye SK, Fong TG, Jones RN, Dillon ST, et al. Apolipoprotein E genotype and the association between C-reactive protein and postoperative delirium: Importance of gene-protein interactions. Alzheimer's Dement. 2020;16:572–80.

51. Adamis D, Meagher D, Treloar A, Dunne C, Larvin M, Martin FC, et al. Phenomenological and biological correlates of improved cognitive function in hospitalized elderly medical inpatients. Arch Gerontol Geriatr. Netherlands; 2014;59:593–8.

52. Adamis D, Rooney S, Meagher D, Mulligan O, McCarthy G. A comparison of delirium diagnosis in elderly medical inpatients using the CAM, DRS-R98, DSM-IV and DSM-5 criteria. Int Psychogeriatr. 2015;1–7.

53. Sepulveda E, Franco JG, Trzepacz PT, Gaviria AM, Viñuelas E, Palma J, et

al. Performance of the Delirium Rating Scale-Revised-98 Against Different Delirium Diagnostic Criteria in a Population With a High Prevalence of Dementia. Psychosomatics. 2015;56:530–41.

54. Bowman K, Jones L, Pilling LC, Delgado J, Kuchel GA, Ferrucci L, et al. Vitamin D levels and risk of delirium. Neurology. United States; 2019;92:e1387–94.

55. Meagher DJ, Leonard M, Donnelly S, Conroy M, Adamis D, Trzepacz PT. A longitudinal study of motor subtypes in delirium: relationship with other phenomenology, etiology, medication exposure and prognosis. J Psychosom Res. 2011;71:395–403.

56. Sepulveda E, Leonard M, Franco JGJG, Adamis D, McCarthy G, Dunne C, et al. Subsyndromal delirium compared with delirium, dementia, and subjects without delirium or dementia in elderly general hospital admissions and nursing home residents. Alzheimer's Dement Diagnosis, Assess Dis Monit. Elsevier; 2017;7:1–10.

57. Oldham MA, Flaherty JH, Maldonado JR. Refining Delirium: A Transtheoretical Model of Delirium Disorder with Preliminary Neurophysiologic Subtypes. Am J Geriatr Psychiatry. 2018;26:913–24.