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E-mail: editorialoffice@wjgnet.com http://www.wjgnet.com

ESPS Peer-review Report
Name of Journal: World Journal of Neurology
ESPS Manuscript NO: 10601
Title: VARIATION IN RISK FACTORS OF DEMENTIA AMONG FOUR ELDERLY GROUPS OF HOSPITALIZED PATIENTS
Reviewer code: 00202286
Science editor: Xiu-Xia Song
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

In this paper, the authors report about the risk factors of dementia among four elderly groups. This is an interesting study. The paper is well written. There are few comments. One of the pitfalls is that the results are not unexpected and similar results have been previously reported. Value of p for Blacks versus Whites is missing. Can the authors briefly comment on the low number of black males in the study? References 18, and 21, should be rewritten. There were some typos that have been corrected and an edited version is attached for the editor.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS
I have reviewed the manuscript WJN-10601 (Variation in risk factors of dementia among four elderly groups of hospitalized patients). The authors attempted to identify risk factors for dementia (focusing on health disorders like diabetes, stroke or other CV morbidity) in the elderly based on their gender and race.
I read the article with interest since I believe the topic is a relevant one. However, I have a number of comments/questions and believe that the article would be appropriate for publishing only after a major revision.
My comments are listed in a random order.
Comments
In the Patients and Methods section, subsection "Data" it is stated that "age adjusted" prevalence rate of dementia was calculated (age standardization based on methodology proposed by CDC). I do not understand the exact purpose of doing this. First – the present study is neither an incidence nor a prevalence study. It is based on an administrative database that records hospitalizations/reimbursement claims. Hence "cases" here are only subjects who were hospitalized during the index period – and NOT ALL elderly within the population who, during the index period, were demented or suffered from any of the comorbidities explored for their relationship with dementia. Therefore, using "cases" identified in this manner for calculation of a "standardized prevalence rate" pertaining to population is – inappropriate (how many "cases" have you missed?). Also – for the purpose of the manuscript – it is completely irrelevant. Or – am I missing some key

element? Unless I am completely wrong, the part about "disease prevalence" (in the Methods and the entire text) – **should be removed**.

This is a cross-sectional study (co-existence of ICD codes pertaining to "dementia" and those pertaining to explored comorbidity is evaluated /retrospectively/ in an administrative database, referring to data collected over 1 year). The analysis, in a large part, is actually the so-called "mediation analysis". Figures 1-5 show typical mediation models in which "predictors" affect the "outcome", either directly or "through" some intermediate variable (mediator). To method allows that "two-stage" coefficients (in this case converted to ORs) are determined to quantify the effect of "predictors" on "mediators", of "mediators" on "dependent variables", and of "predictors" on "dependent variables" with decomposition of the total effect into a "mediated" and a "direct" (non-mediated by the tested mediators) one. HOWEVER – mediation analysis essentially resides on the 2 assumption of "causality" and, consequently, it assumes (this is ESSENTIAL) that there is an adequate "temporal" relationship between potential "predictors" ("causes") and "intermediate consequences" ("mediators") and, finally, "final consequences" (dependent variables) – simply, for a meaningful mediation analysis, it must be RELIABLY ESTABLISHED that the "cause" preceded the "consequence". This is IMPOSSIBLE with cross-sectional data. The entire concept of the presented analysis resides upon an assumption that, for example – dyslipidemia existed BEFORE dementia, that hypertension existed before dementia…etc., and that they, potentially, contributed to occurrence of dementia. But – why not think this way: dementia is a risk factor for hypertension? Etc. Some prospective cohort studies have clearly demonstrated that dementia IS A RISK FACTOR for stroke, heart failure etc. And with cross-sectional data, both ways of thinking are equally justified – that co-existence between, e.g., dementia and stroke is due to the fact that dementia is a risk factor for stroke, and also *vice-versa*.

Overall, mediation analysis is only appropriate for prospective studies or other designs that can UNEQUIVOCALLY demonstrate the needed temporal pattern of occurrence of predictors, mediators and dependents. **Hence, it should be completely removed from this manuscript**.

Besides the fact that I am convinced that mediation analysis should be removed, I need to comment briefly on presentation of the method employed for the presented analysis. To my knowledge, there are some "ready to use" computer programs for mediation analysis of data where independents, mediators and dependents are all binary – e.g., macros for implementation in SAS or SPSS. However, to the best of my knowledge, these macros CANNOT accommodate for covariates (unlike some other programs intended for continuous dependents). Figures 1-5 show several "predictors" one "mediator" and a "dependent". How were the coefficients for individual "predictors" obtained? In multivariate models (all predictors entered simultaneously in order to estimate "independent" associations)? Or…? If these figures just "compile" coefficients from individual runs with individual predictors – then they are ADDITIONALLY inappropriate. Finally, it is accustomed to specify, in the Methods section: the software used and, if models are generated by the authors – to explain and elaborate the models.

Having established that the mediation analysis is inappropriate, what remains is the question about

"different associations (between dementia and CV&metabolic comorbidity) across gender and race, i.e., across the gender-by-race subsets". The authors employed four 3 separate analyses – one by gender-by-race subset. These subsets differed in size. Different patterns of "significance" (of associations) within these subsets were observed. And authors concluded that, in respect to gender-by-race – there are different risk factors for dementia. This is a rather naïve approach to the problem. First, the question of causality is highly problematic in this setting, as explained. Second, the problematic issue is also a "comparison" of effects from 4 different analyses. On top of that, the four subject subsets differed in size. It is clearly obvious that "an effect not reaching statistical significance" in a set of 300 subjects, could attain it in a set of 2000 subjects. But this is not the main issue. The main issue is that comparison of estimates from different analyses – is problematic. At bets, it could be perceived as "indicative" or "hypothesis generating", but definitely not conclusive. A much higher level of "comparability" of different effects (across subsets) would be obtained from a SINGLE MODEL with interaction terms. For example, "dementia" (yes/no) is a dependent variable; actual age, sex, race, hypertension, diabetes, stroke, heart failure, dyslipidemia etc. are independent variables. This model would test for independent effects of: sex, race and all other independents. A model to test for differences of the effects of gender*race subsets would include an interaction term – gender*race. The contrasts arising from this interaction would allow for testing, for example,:a) the effect of race at a given sex (while controlling for all other covariates); b) the effect of sex at a given race (while controlling for all other covariates; c) the overall effect of sex (controlling for covariates); d) overall effect of race (controlling for covariates). A model to test the effect of, for example, stroke by race, would include an interaction term – stroke*race; and for the effect of stroke by gender*race, would include an interaction term stroke*gender*race. Appropriate specification of the models would then allow for determination of a DIFFERENCE in the effect of stroke between, e.g., white men and black women, etc. And so on.

Alternatively, four separate multivariate models could be used in the four subsets (B-F, B-M, W-F, W-M), with all the potential "predictors" entered to detect independent associations. And then a HIGH LEVEL of caution introduced in data interpretation – using terms such as "indicate" or "suggest".

Considering the structure of data at hand and the actual objective (indicate different "grouping" of comorbidities with dementia depending on gender and race), probably the best data analysis approach would be – cluster analysis: to simply see how do these variables "group" or "cluster". The result would be of the type: "cluster 1: male sex, black race, dementia, stroke, diabetes"; "cluster 2: male sex, white race, stroke, hypertension 4 dementia" etc. And Discussion would then be focused on potential meaning/reasons for the observed clustering. The Methods section should be clearer (than it is now) and Abstract revised according to the actual results.