Reviewer’s report

Title: Prevalence of at-risk genotypes for genotoxic effects decreases with age in a randomly selected population in Flanders: a cross sectional study.

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Reviewer: Domenico Franco FM Merlo

Reviewer’s report:

Major Compulsory Revisions

Methods

study population:
The authors describe the study population (1583 adults and 1679 adolescents) as being selected at random within the Flemish Environment and Health Survey (FLEHS). As stated there was some self-selection in participation of the adults in the study due to fact that traveling to local community centres was required and sick people may have been self excluded. However it is not clear from the manuscript how many of the randomly selected did participate in the study. In page 8 the study subjects are indicated as selected as well as participants.

I suggest to include a simple table (or chart) showing (among adults and adolescents) the numbers of “randomly selected”, the number (and %) of participants and non participants and the numbers (and %) of available DNA. This will help the readers to understand the magnitude of self selection and the consequences on the results and their interpretation.

Selection of Polymorphisms and Genotyping and Results

19 genes and 28 low penetrance polymorphisms were selected a priori based on commonly studied “susceptibility” genes involved in xenobiotic metabolism, oxidative stress defense and DNA repair. These genes have been reported in the literature as being associated with probability of being sick (from a variety of diseases, mainly chronic diseases such as cancer). The authors state that for these genes a clear ‘increased risk’ or a ‘protective effect’ was reported on the available literature. This is the correct approach to identify the study hypotheses. An index was generated for each gene polymorphism/alleles and a sum of risk alleles was computed for all polymorphisms to generate indexes that were used in the statistical analyses to compare the proportions of adolescents and adults carrying the “sum of gene/alleles” and the “gene-grouped” into 4 “biological processes” (i.e., biotransformation phase I, biotransformation phase II, oxidative stress, and DNA repair) separately.

This type of analysis, has the advantage of showing the study findings collapsed into 4 groups (+ the sum of gene/alleles) but has the disadvantage of hiding the differences in proportions of each of the 19 genes between adolescents and adults.
I suggest the authors to report a table for each of the 19 genes/alleles (as reported in Table 1) with the n and % for adolescents and adults. This table will have the advantage of showing the frequency distribution of each of 19 genes/alleles in the study populations and allow readers to inspect the data. There is no need to perform statistical comparisons in such table.

The summary of the findings (Table 2) should include the number of subjects and the %, not only the latter and the mean number of risk alleles. As it is now it is not fully informative and there is no corresponding data for mean number of risk alleles to which the authors refer in the results section.

Minor Essential Revisions

Discussion:
As stated, the hypothesis that higher sensitivity to genotoxic agents- decreases with age among persons capable and willing to participate in a biomonitoring study, seems reductive. The real hypothesis is tested among those capable and willing to participate in an a study but concern the general population (isn’t the FLEHS a Stratified Clustered Multi-Stage Design?). Please just say “….decreases with age”.

do not think it is correct to state that the results “..suggest that Flemish residents carrying more unfavorable genetic traits related to genotoxic effects were more likely to be severely ill or to have died before age 50 to 65”. The correct conclusion is that more unfavorable genes are detected in adults aged 50 to 65 than in adolescents. This may be interpreted as resulting from a higher mortality among subjects with unfavorable genetic traits. Then the discussion that follows is reasonable.

Conclusion:
According to the previous comment, replace the statement “…in a randomly selected population of persons able and willing to participate in a biomonitoring study” with “in a randomly selected Flemish population”.

Discretionary
It would interesting if the authors could attempt to quantify the proportion of deaths attributable to the differences in % between adolescents and adults detected. Indeed the leading causes of death do differ in adolescent and adults and it is not necessary true that the main causes in the age group not included in the study (17-49 years old) are related to the genotypes considered.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? NO

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? NO

Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? NO

Do you have any other financial competing interests? NO

Do you have any non-financial competing interests in relation to this paper? NO

I declare that I have no competing interests.