STROBE Statement—checklist of items that should be included in reports of observational studies

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|  | Item No. | Recommendation | Page  No. | Relevant text from manuscript |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | 5 | “baseline and longitudinal change in cognitive performance”. “Cognitive performance was measured at baseline visit and first follow-up”. |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 5-6 | Methods: 10 lines.  Results, Conclusions: 8 lines. |
| Introduction | | | |  |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 7 | First 3 paragraphs |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 7-8 | One paragraph |
| Methods | | | |  |
| Study design | 4 | Present key elements of study design early in the paper | 8 | “HANDLS is an ongoing prospective cohort study”… |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 8 | “Initiated in 2004”, baseline age:30-64y, Baltimore, MD. |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 9-10 | “Study Sample” section and Figure 1 participant flowchart. |
| (*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed  *Case-control study*—For matched studies, give matching criteria and the number of controls per case | N/A |  |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 10-13 | Cognitive assessment, DNA methylation and Covariate sections |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 13-15 | Statistical analysis section,  Supplemental Method 1, Supplemental Method 2 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 14 | Third paragraph: “Selection bias ….” |
| Study size | 10 | Explain how the study size was arrived at | 15 | Results: First paragraph, Figure 1, Table S1. |

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| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 14 | Statistical analysis part. |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 14 | “Covariates included in the overall model…. Covariates Section”. |
| (*b*) Describe any methods used to examine subgroups and interactions | 14 | “Models were presented for the overall eligible sample and stratified by sex…. and TIME”. |
| (*c*) Explain how missing data were addressed | 14 | “Selection bias … covariate”  “We assumed unavailability of outcomes to be missing at random (Supplemental Methods 2). |
| (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed  *Case-control study*—If applicable, explain how matching of cases and controls was addressed  *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | 14 | “Selection bias … covariate”  “We assumed unavailability of outcomes to be missing at random (Supplemental Methods 2). |
| (*e*) Describe any sensitivity analyses | 15, 17 | “A sensitivity analysis was also conducted by including only statistically significant covariates in the final models. “  “In a sensitivity analysis … Epiclock3×Time”… |
| Results | | | | |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 9-10 |  |
| (b) Give reasons for non-participation at each stage | 9-10 |  |
| (c) Consider use of a flow diagram | Figure 1 |  |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |  |
| (b) Indicate number of participants with missing data for each variable of interest | Figure 1 |  |
| (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | 5 | Mean follow-up time: ~4.7y |
| Outcome data | 15\* | *Cohort study*—Report numbers of outcome events or summary measures over time | Tables 2-3, Table S2 |  |
| *Case-control study—*Report numbers in each exposure category, or summary measures of exposure | *n/a* |  |
| *Cross-sectional study—*Report numbers of outcome events or summary measures | *n/a* |  |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Table 2-3, S2 |  |
| (*b*) Report category boundaries when continuous variables were categorized | n/a |  |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | n/a |  |

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| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 17 |  |
| Discussion | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 17-18 | “Our study … p=0.007).” |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 22 | “Nonetheless, …. Meta-analysis” |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 23 | “Our study findings …. Our cognitive decline” |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 23 | “Interventions…. Our findings” |
| Other information | |  | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 2 | Sources of funding. |

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.