Concept Paper Template

Provisional Paper Title: Autistic traits and health, mediated by loneliness, sleep quality, and mental health? A Dunedin study.

Proposing Author: Francesca Happé

Co Authors: Temi Moffitt, Avshalom Caspi, Dunedin team, David Mason (PhD student), Angelica Ronald (others as advised by Temi and Avshalom), Richie Poulton (Dunedin Study Director), Sandhya Ramrakha (Research manager of Phase 45 data collection), Renate Houts (biostatistician who will derive variables and carry out reproducibility check of final results)

Author's Email: francesca.happe@kcl.ac.uk

P.I. Sponsor: Temi Moffitt
(if the proposing author is a student or colleague of an original PI)

Today's Date:

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

Background and gaps in the literature

In our previous analyses of age 45 Dunedin data, we found that higher autistic traits were associated with a faster pace of aging, older facial age, and poor self-, informant-, and interviewer-rated health (whilst controlling for sex, childhood IQ and childhood SES). This was the case whether taking a dimensional approach or when examining those scoring above vs below the trait measure (AQ-10) cut-off. These findings in high autism trait adults fit with reports of poorer physical health in diagnosed autistic adults in middle and older age.

In our paper we proposed four possible explanations for the observed association between autistic traits and pace of ageing and physical health:

1) a possible genetic mechanism underlying both autistic traits and faster aging;
2)autism-related lifestyle factors, such as poorer social networks, which may affect health-related behaviours;
3)commonly cooccurring difficulties in autism, such as sleep problems, which may affect aging and health;
4)social disadvantage, due to prejudice and victimization, and adverse life

experiences that likely increase allostatic load, thereby speeding up the aging process.

We would like to test two of these hypotheses further, by carrying out follow-up analyses with relevant constructs as potential mediators between autistic traits and health/aging outcomes. This CP sets out plans to explore explanations 2 and 3 above (hypothesis 1 will be explored in later proposed work).

We would like to make the case that we can treat autistic traits as relatively stable in adulthood, and hence treat the AQ-10 data collected at age 45 as a measure of lifelong autistic traits. That would enable us to examine a causal account of autistic traits (pre age 38) with mediators from age 38 (e.g. loneliness and sleep quality), and health/aging outcomes at age 45 (whilst controlling for childhood SES, childhood IQ, and gender). We believe this is a plausible assumption. This is because autistic traits have been shown to be remarkably stable in cohorts that cover childhood into early adulthood, and it seems reasonable to assume this stability lasts throughout adulthood. Autism characteristics measured by the AQ have been shown not to be strongly associated with age in a cross-sectional study of adults (Lodi-Smith et al 2021).

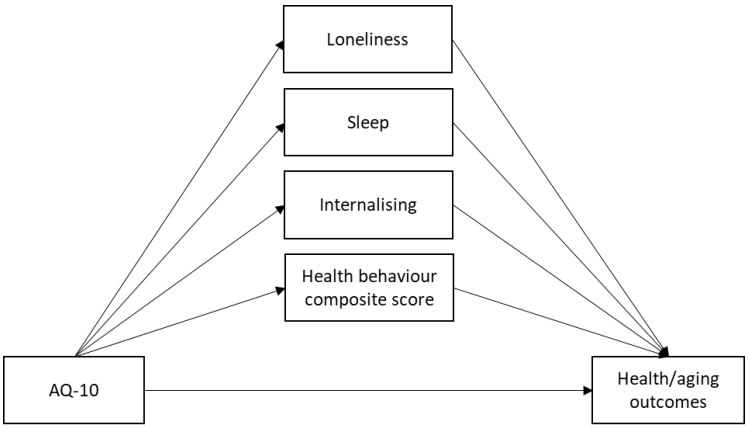
Aims and objectives:
The aim of this study is to test whether the association between autistic traits and physical health and the pace of ageing in midlife, is mediated by loneliness, sleep quality, internalizing symptoms, and/or health behaviours controlling for covariates (sex, childhood SES, childhood IQ).

Objective
1. We propose to develop our initial analyses by specifying loneliness (ULCA total score), sleep quality (PSQI total score), internalising symptoms, and health behaviours as mediators between AQ-10 total score and health/aging outcomes.

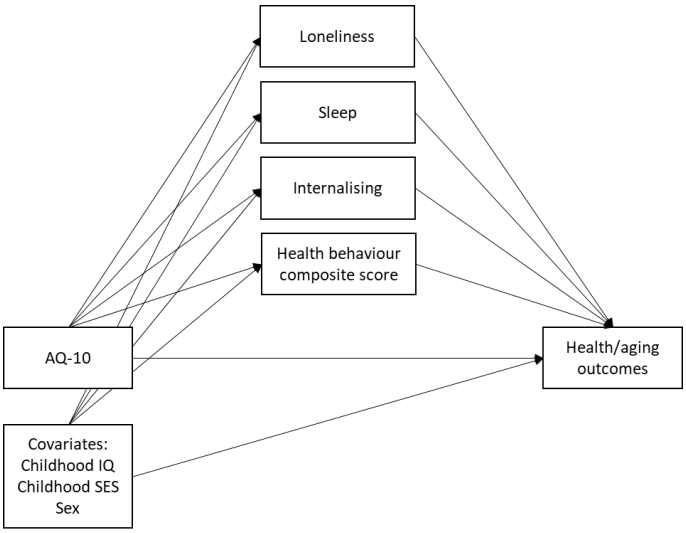
Data analysis methods:

Data from the AQ-10 will be used to take a dimensional approach. All distributions will be checked, and where necessary, variables may be transformed to approximate normality.

Our main analysis will examine if our hypothesized variables mediate the association between AQ-10 score and health/aging outcomes. We propose a non-ordered mediation analysis whereby all mediators are entered into the same model, whilst controlling for childhood IQ and childhood SES. First, we will analyse a mediation model, without any covariates, to estimate the direct and indirect effects of AQ-10 score on each outcome:



Second, we will test the same models with covariates included:



Here, we have paths from each covariate to each mediator and outcome, so an effect (direct or indirect) between AQ-10 and each outcome is fully adjusted for childhood IQ and SES, and sex.

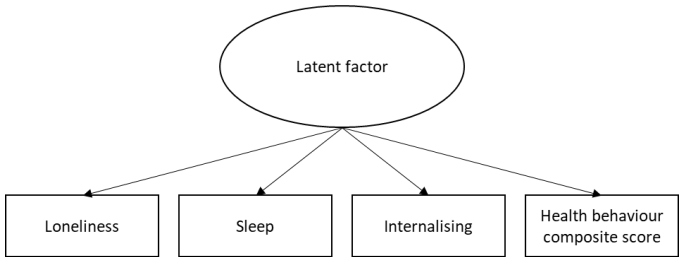
To minimize the number of models, and potential issues with multiple comparisons, we propose to run the above two models using three outcome variables: pace of ageing, facial age, and a composite health outcome (combining self-, informant-, and interviewer-rated health scores). Thus, we will estimate 6 models.

Exploratory analysis with a latent variable

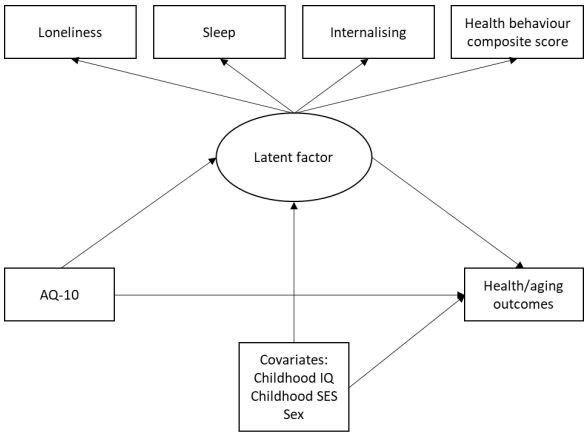
It is plausible that our mediators are interrelated, for example sleep quality may be associated with health behaviours, and loneliness may be associated with internalizing behaviours. If this is the case, it may be interesting to explore a latent variable model, where we model the mediators as indicators of an underlying latent factor. This has some advantages in that it is more parsimonious, as it will have fewer paths to estimate. Also, if we find a mediation effect, then the factor loadings from the latent factor to the indicators will

identify the relative contribution of each indicator to the mediation effect. We can still try to estimate the amount of variance unexplained by the latent factor, which may help generate hypotheses about other missing mediators or mechanisms. A potential drawback to this approach could lead to uncertainty about interpreting the latent factor. It could represent an over-arching 'maladaptive behaviour' factor.

To do this, we would first fit a measurement model, comprising just the latent factor and the four indicators:



This will be used to establish if the latent factor, with these four indicators, is a good fit to the data. If so, we can then incorporate this latent variable into the mediation model:



Note, this analysis will only be carried out if the mediators are moderately inter-correlated ($r>0.2$). Otherwise, we will only estimate the path analysis models.

Variables needed at which ages:

Age 45
AQ-10, pace of ageing, facial age, composite health score (of self-, informant-interviewer, we would also request the individual scores – for descriptive statistics reporting).

Age 38
UCLA total score, PSQI total score, interalising total score, health behaviour total score (smoking status, physical activity, diet, and alcohol consumption, from Lourida et al., 2019).

Covariates:
Gender
SES in childhood
Cognitive functioning, in childhood (WAIS IQ)

Significance of the Study (for theory, research methods or clinical practice):

Identifying possible mediators between autistic traits and pace of ageing/poor health could give intervention targets for improving health outcomes. For example, if sleep or loneliness mediate the relationship, these would become important treatment targets in order to improve health and slow ageing for adults with high autistic traits

Data Security Agreement

Provisional Title	Why is physical health and the pace of ageing worse for adults with high autistic traits?
Proposing Author	Francesca Happé, David Mason, Angelica Ronald, Temi Moffit, Avshalom Caspi
Today's Date	November 2021

Please keep one copy for your records and return one to the PI Sponsor

Please initial your agreement: (customize as necessary)

FH	I am current on/will refresh my Human Subjects Training [CITI www.citigrogram.org] or equivalent.
FH	My project is covered by the Dunedin Study's ethics approval OR I have /will obtain ethical approval from my home institution (please specify).
FH	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: • encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) • password-protected • configured to lock-out after 15 minutes of inactivity AND • has an antivirus client installed as well as being patched regularly.
FH	I will not "sync" the data to a mobile device.
FH	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact my PI Sponsor or Study Director
FH	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
FH	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to your PI Sponsor or Richie Poulton for strategies for achieving compliance with data-sharing policies of journals.*
FH	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: