Methodological challenges in life course studies

George B. Ploubidis & Bianca DeStavola

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Outline

- Methodological challenges in life course studies
- Two examples
- Some suggestions
“A life course approach is paradoxical as on the one hand it is intuitively obvious … and yet on the other it is empirically complex”

Kuh and Ben-Shlomo, 2004
I would add

Methodologically complex too….
Major methodological challenges

- Missing data
- Measurement error
- Unmeasured confounding
More challenges

- Life course mechanisms (accumulation, chains of risk, critical period, social drift) imply a mechanistic view of causality
- The process of reversibility implies both mediation and moderation
- All the hypothesised effects require the formal estimation and reliable quantification of direct, and indirect effects, as well as moderated mediation and/or interactions
More challenges

- Repeated measures a strength of life course studies
- However, quantifying change and in particular parallel processes is not so straightforward
- If homogeneity over time is assumed then models that describe change with 1 – 2 parameters (single curve/trajectory) can be used (GEE, Multilevel models, Growth curve models)
- If the longitudinal patterns show evidence of heterogeneity some form of a mixture model can be used
- Either approach brings in additional assumptions and challenges (modelling time varying covariates and/or confounders for example)
Lifelong Socio Economic Position and biomarkers of later life health: Testing the contribution of competing hypotheses

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ABSTRACT

The relative contribution of early or later life Socio Economic Position (SEP) to later life health is not fully understood and there are alternative hypotheses about the pathways through which they may influence health. We used data from the English Longitudinal Study of Ageing with a formal approach for the identification of mediating factors in order to investigate alternative hypotheses about life course influences on biomarkers of later life health. We found that early life SEP predicts physical health at least 65 years later. However, a more complicated pattern of associations than that implied by previous findings was also observed. Age group specific effects emerged, with current SEP dominating the effect on later life physical health and fibrinogen levels in participants under 65, while early life SEP had a more prominent role in explaining inequalities in physical health for men and women over 75. We extend previous findings on mid adulthood and early old age, to old age and the beginnings of late old age. The complexity of our findings highlights the need for further research on the mechanisms that underlie the association between SEP and later life health.

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Background

- In European countries with old age structures older people account for the majority of those in poor health.
- Substantial inequalities in the health of different socio-economic groups persist in old age.
- It has recently been shown that the economic costs of socioeconomic inequalities in health are in the order of €1000 billion, or 9.4% of European GDP.
These observations suggest a particular need to investigate the influence of Socio Economic Position (SEP) on the well being of the older population.

There is a great potential for shifting the overall distribution of risk and improving average population health by eliminating or reducing the socioeconomic health gradient.
We have limited scientific evidence on the individual and macro level mechanisms that underlie socio economic inequalities in health.

Although interventions on the exposure (SEP) are welcome, intervening on the mechanism that links SEP and health is a more realistic target.

In the current climate of financial austerity, efficient and cost effective policies are needed.
A more tractable problem

Early life SEP

Early Life Health

Later life SEP

Later Life Health

following lives from birth and through the adult years
Chains of risk

- Early life SEP
- Later life SEP
- Later life Health

following lives from birth and through the adult years
Childhood/Early life
Accumulation

Early life SEP

Later life SEP

Later life Health

following lives from birth and through the adult years
Social drift

Early Life Health → Later life SEP → Later life Health

following lives from birth and through the adult years

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Aims

- The major aim of the present study is to test the relative contribution of these hypotheses to later life health inequalities.
- A first step in understanding the mechanism that underlies the association between SEP and health.
- We need to assign reliable parameters to all these hypotheses – it’s all about mediation!!
Causal Mediation

- Assigning reliable parameters and standard errors to direct and indirect effects is not so straightforward, especially if mediators and/or outcomes are binary/ordinal
- Natural vs controlled direct/indirect effects
- If interactions are present, they need to be taken into account
- Causal mediation provides meaningful quantities (parameters) that potentially have causal properties under certain assumptions
- Quantities derived from traditional methods do not have a causal interpretation under any assumption
- Within linear systems LSEMs can be used to formally quantify direct and indirect effects (actually all available methods give identical results)
- With binary outcomes and/or mediators other options such as G estimation, the G formula or Inverse Probability Weighting should be used
Not a free lunch

- Stronger assumptions about unmeasured confounding are needed for each additional mediator or moderator in the DAG.
- Within LSEM more than one mediators can be handled
- However, if the mediator and/or outcome are not continuous only one mediator can be handled (even in theory)
- A theoretical and practical issue
- Endogenous confounding, or the potential association of the exposure with a mediator – outcome measured confounder (the kite) can only be handled within LSEM
Sample

- We used data from the English Longitudinal Study of Ageing (ELSA), a nationally representative multi-purpose sample of the population aged 50 and over living in England.
- We analysed a partially incomplete dataset (N = 7758), in which participants were included if they had at least one non missing observation in early life SEP indicators (ELSA Life history interview).
- Stratified by gender and age group (50-64, 65-74, 75+).
Measures

ELSA Life history interview – 2007

- Recollection of early life SEP (Age 10)
- Recollection of early life health (childhood - adolescence)
Recollection of early life SEP (age 10)
ELSA Life History Interview – Wave 3

- Chronic Illness Depression
- 0.076
- -0.101
- Early life SEP
- 0.615
- Housing tenure
- 0.446
- Household amenities
- 0.656
- Number of books at home
- 0.503
- Crowding

following lives from birth and through the adult years

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Recollection of early life health
ELSA Life History Interview - Wave 3

Early life Health

- Chronic Illness
- Depression

Self reported health

Missed school > 1 month

Physical activities restricted > 3 months

Confined to bed > 1 month

> 3 inpatient stays in one year

0.519
0.930
0.832
0.920
0.749
Fibrinogen is the major coagulation protein in blood by mass; it is the precursor of fibrin and an important determinant of blood viscosity and platelet aggregation. Fibrinogen level is associated with an approximate doubling in risk of major cardiovascular disease outcomes (such as coronary heart disease and stroke) and of aggregate nonvascular mortality (mainly comprising cancer deaths).

Confounders

• Age, retirement status, marital status, number of children and cognitive ability were included in the structural model
Statistical modelling

- The specification of each of the latent dimensions was carried out with models appropriate for combinations of binary, ordinal and continuous indicators
- A LSEM was then estimated in order to jointly model the predictors, mediators and health outcomes (adjusted for confounders)
- Preliminary results showed no evidence of interactions
- Missing data on Wave 4 mediators and health outcomes handled with FIML assuming a MAR mechanism
- Estimation with MLR in Mplus 6.12
Early life SEP = a
Chains of risk = b*c
Accumulation = a + c
Social drift = d*c
Total effect of Early life SEP = a + (b*c)
Results - Physical Health

The graph illustrates the physical health status across different age groups and gender. The y-axis represents the physical health measure, while the x-axis shows age groups and gender. The graph includes several categories for comparison:

- SEP Later life (W4)
- SEP Age 10
- Chains of risk
- Total Early life SEP
- Accumulation
- Social drift

The data is segmented by age groups (50-64, 65-74, 75+) and gender (Men, Women). The bars indicate the average physical health scores with error bars showing the variability. The graph provides insights into how different factors influence physical health across various demographics.
Results - Fibrinogen

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- SEP Later life (W4)
- SEP Age 10
- Chains of risk
- Total Early life SEP
- Accumulation
- Social drift
Sensitivity analysis

- Nice parameter estimates, but sequential ignorability implies no unmeasured confounders
- Sufficiently approximated* for the later life SEP – health association, but not for other parts of the DAG
- No data on parental characteristics such as cognitive ability and health status
- Results could reflect the effect of unmeasured parental characteristics
Sensitivity Analysis
Strong confounding scenario

following lives from birth and through the adult years
Physical health sensitivity analysis
Fibrinogen sensitivity analysis
We have included possible confounders of the later life SEP physical health/fibrinogen associations, but how about running some more sensitivity analyses?
Medsens (Stata, R, Mplus)

- Employs the correlation between the residual variances (errors) of the models for the mediator and outcome
- Effects are computed given different fixed values of the residual covariance.
- The proposed sensitivity analysis asks the question of how large does Rho have to be for the mediation effect (Average Causal Mediation Effect – ACME) to disappear.
Medsens Results

ACME(\(\rho\))

95% Conf. Interval

Sensitivity parameter: \(\rho\)
Summary

- Physical health more socially patterned than fibrinogen
- Accumulation, chains of risk and early life/childhood hypotheses confirmed
- No support for the social drift hypothesis
- Cohort and gender differences emerged with respect to the relative contribution of the confirmed hypotheses
Accumulation of risk was dominated by the effect of later life SEP in those under 75.

Early life SEP (Critical period & Chains of risk) had the most prominent effect in those over 75.

Later life SEP the sole contributor to later life inequalities in fibrinogen levels.

Early life SEP more important for women.
Explanations?

- Ageing process: younger cohorts expected to exhibit similar patterns of associations as they grow older.
- Cohort specific effects due to the observed differences in early life SEP. Lower Early life SEP of older cohorts supports this idea. Those over 75 were born during the great depression of the 1930’s.
- Selection: Over 75’s a selected sample of higher SEP within cohort survivors. Less SEP variance in this group supports this explanation.
Limitations

- Observational data – Causal inference a nearly alchemic task
- However, sensitivity analyses where confounders were simulated supported our results – but bias due to unknown unmeasured confounders cannot be ruled out
- Sensitivity parameters dependent on distribution of exogenous unmeasured confounder(s) – not identified non parametrically
- Retrospective data, only two timepoints
Another example

Life course partnership status and biomarkers in mid-life: Evidence from the 1958 British birth cohort

George B. Ploubidis, Richard J. Silverwood, Bianca DeStavola & Emily Grundy
Background

- Previous studies have shown that marital status is associated with health outcomes and mortality.
- With a few exceptions studies of marital status and health have considered only current marital status or transitions over relatively short periods.
- The accumulated benefits and risks of marital status trajectories over the lifecourse have not being studied.
Furthermore, only a few studies have considered the association between non-marital cohabitation and health, a topic of increasing importance given that non-marital cohabitation is becoming more common.

Of those studies which have used measures of health, most have employed self-reported measures.

In the few studies where objective health indicators were used, sample sizes were relatively small.

In this study we are employing a population based birth cohort and a modelling approach that allows us to capture stability as well as change in partnership status over the lifecourse.
Objectives

- Investigate the cumulative effect that different trajectories of partnership status over the life-course have on biomarkers in mid-life

- To what extend smoking accounts for the association between life course partnership status and biomarkers in mid-life?
The British 1958 birth cohort includes all persons born in England, Scotland and Wales during one week in March 1958.

Cohort members have been followed-up periodically from birth into adulthood. Our outcomes are derived from the clinical examination in their home undertaken in 2002 – 2004.

Marital status and cohabitation have been recorded from sweep 4 (1981) when participants were 23 years old.

We are using data from sweep 4 (1981, age 23), sweep 5 (1991, age 33), sweep 6 (2000 age 42) and the biomedical survey (2002-2004 age 44 – 46) to derive the partnership status trajectories.

Early life SEP and health are derived from sweeps 0 – 3 (ages 1 – 16).
Measures I

Outcomes:
- Inflammatory and haemostatic biomarkers: Fibrinogen, C – Reactive Protein (CRP), Von Willebrand Factor (VWF), Tissue plasminogen activator antigen (TPA) and Fibrin D- dimer (Ddimer).
- Metabolic syndrome: MS was characterized using the International Diabetes Federation definition
- Respiratory function: Scores on Force Vital Capacity - the maximum amount of air a person can expel from the lungs after a maximum inhalation.

Measured confounders:
- All models adjusted for early life SEP, cognitive ability @ 10, early life health status, education @ 23, self reported health status @ 23, BMI @ 23 and various lab processing related variables.
Measures II – Partnership status indicators

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Missing data - Rubin’s framework

**Missing Completely At Random (MCAR)**
- Almost impossible in life course studies, some variables are known causes of attrition – partially testable
- In the 1958 cohort early life characteristics influence attrition
- Complete case analysis and non principled approaches (mean imputation, last observation forward) will likely be severely biased

**Missing At Random (MAR)**
- Implies that if all the variables that are responsible for the missing data generating mechanism are complete and included in the model, this "mechanism" can be ignored - Principled apaches (MI, FIML, IPW)
- Conditional ignitability is a reasonable assumption for life course studies

**Not Missing At Random (NMAR)**
- More complex scenario, solutions only for models with repeated measures. Pattern mixture model, Dingle – Kenward selection model.
Early life
SEP, Health, Cognitive ability

Education @ 23

Health, BMI @23

Partnership Status 23 - 42

Biomarkers @ 42

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• Longitudinal Latent Class Analysis – Semi parametric model, introduces a discrete latent variable to capture common variation in the observed marital status and cohabitation indicators
• Forms latent classes - groups (trajectories) based on the pattern of responses to the observed indicators
• Captures heterogeneity – does not assume a single rate of change/single curve for all
• A data reduction method - in theory the number of possible response patterns in theory is $5^2 = 512$.
• However since participants who are married cannot simultaneously be non – married cohabiters, there are three responses available at each wave
• Distinct response patterns $2 \times (3^4) = 162$
• In this instance LCA is used to summarise these patterns creating longitudinal profiles in a parsimonious way that can be used in further analysis with appropriate link functions for the nature of the outcomes (linear and logit models)
• All models in Mplus 7.0, estimated with MLR, Monte Carlo integration.
• Missing data handled with FIML assuming MAR
### Results I – Model selection

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following lives from birth and through the adult years
following lives from birth and through the adult years
following lives from birth and through the adult years
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<td>9 Classes</td>
<td>89</td>
<td>-14476.328</td>
<td>29130.656</td>
<td>29713.489</td>
<td>29430.677</td>
<td>0.933</td>
<td>97.286</td>
<td>0.001</td>
</tr>
<tr>
<td>10 Classes</td>
<td>99</td>
<td>-14436.959</td>
<td>29071.918</td>
<td>29720.239</td>
<td>29405.650</td>
<td>0.938</td>
<td>78.737</td>
<td>0.001</td>
</tr>
</tbody>
</table>
following lives from birth and through the adult years
following lives from birth and through the adult years

Women

Class 1 (N = 2168, 42.0%)
Remarried probability: 0.139

Class 2 (N = 1199, 23.2%)
Remarried probability: 0.121

Class 3 (N = 415, 8.0%)
Remarried probability: 0.080

Class 4 (N = 291, 5.6%)
Remarried probability: 0.659

Class 5 (N = 446, 8.6%)
Remarried probability: 0.316

Class 6 (N = 641, 12.4%)
Remarried probability: 0.024

www.cls.ioe.ac.uk
## Results - Men

<table>
<thead>
<tr>
<th></th>
<th>Fibrinogen</th>
<th>CRP</th>
<th>VWF</th>
<th>TPA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class1</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Class2</strong></td>
<td>0.019</td>
<td>0.131</td>
<td>0.029</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>Class3</strong></td>
<td>0.010</td>
<td>-0.013</td>
<td>-0.001</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>Class4</strong></td>
<td>0.008</td>
<td>0.008</td>
<td>0.003</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Class5</strong></td>
<td>0.028</td>
<td>0.064</td>
<td>-0.006</td>
<td>0.045</td>
</tr>
<tr>
<td><strong>Class6</strong></td>
<td>0.034</td>
<td>0.148</td>
<td>0.020</td>
<td>0.061</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Ddimer</th>
<th>Metabolic Syndrome</th>
<th>FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class1</strong></td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Class2</strong></td>
<td>0.035</td>
<td>0.756</td>
<td>0.071</td>
</tr>
<tr>
<td><strong>Class3</strong></td>
<td>0.043</td>
<td>1.067</td>
<td>-0.112</td>
</tr>
<tr>
<td><strong>Class4</strong></td>
<td>0.054</td>
<td>1.077</td>
<td>-0.076</td>
</tr>
<tr>
<td><strong>Class5</strong></td>
<td>0.016</td>
<td>0.759</td>
<td>0.050</td>
</tr>
<tr>
<td><strong>Class6</strong></td>
<td>0.038</td>
<td>0.867</td>
<td>-0.130</td>
</tr>
</tbody>
</table>
## Results - Women

<table>
<thead>
<tr>
<th></th>
<th>Fibrinogen</th>
<th>CRP</th>
<th>VWF</th>
<th>TPA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class1</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Class2</strong></td>
<td>-0.018</td>
<td>-0.035 to -0.002</td>
<td>-0.087</td>
<td>-0.186 to 0.011</td>
</tr>
<tr>
<td><strong>Class3</strong></td>
<td>0.001</td>
<td>-0.023 to 0.023</td>
<td>-0.032</td>
<td>-0.173 to 0.110</td>
</tr>
<tr>
<td><strong>Class4</strong></td>
<td>0.010</td>
<td>-0.018 to 0.038</td>
<td><strong>0.195</strong></td>
<td><strong>0.028 to 0.361</strong></td>
</tr>
<tr>
<td><strong>Class5</strong></td>
<td>-0.012</td>
<td>-0.037 to 0.014</td>
<td>-0.013</td>
<td>-0.161 to 0.134</td>
</tr>
<tr>
<td><strong>Class6</strong></td>
<td><strong>0.028</strong></td>
<td><strong>0.006 to 0.050</strong></td>
<td>0.029</td>
<td>-0.104 to 0.162</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Ddimer</th>
<th>Metabolic Syndrome</th>
<th>FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class1</strong></td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Class2</strong></td>
<td>-0.002</td>
<td>-0.048 to 0.043</td>
<td><strong>0.54</strong></td>
</tr>
<tr>
<td><strong>Class3</strong></td>
<td>0.016</td>
<td>-0.046 to 0.079</td>
<td><strong>0.673</strong></td>
</tr>
<tr>
<td><strong>Class4</strong></td>
<td>-0.037</td>
<td>-0.105 to 0.031</td>
<td><strong>1.043</strong></td>
</tr>
<tr>
<td><strong>Class5</strong></td>
<td>-0.064</td>
<td>-0.131 to 0.002</td>
<td><strong>0.778</strong></td>
</tr>
<tr>
<td><strong>Class6</strong></td>
<td>-0.012</td>
<td>-0.070 to 0.047</td>
<td><strong>0.776</strong></td>
</tr>
</tbody>
</table>

<sup>following lives from birth and through the adult years</sup>
Causal Mediation

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Direct Effect (CDE)</td>
<td>0.024</td>
<td>0.002 to 0.046</td>
<td></td>
</tr>
<tr>
<td>Natural Direct Effect (NDE)</td>
<td>0.024</td>
<td>0.002 to 0.046</td>
<td></td>
</tr>
<tr>
<td>Natural Indirect Effect (NIE)</td>
<td>0.090</td>
<td>0.004 to 0.014</td>
<td></td>
</tr>
<tr>
<td>Total Effect</td>
<td>0.033</td>
<td>0.011 to 0.055</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Direct Effect (CDE)</td>
<td>0.033</td>
<td>0.011 to 0.055</td>
<td></td>
</tr>
<tr>
<td>Natural Direct Effect (NDE)</td>
<td>0.033</td>
<td>0.011 to 0.055</td>
<td></td>
</tr>
<tr>
<td>Natural Indirect Effect (NIE)</td>
<td>0.007</td>
<td>0.004 to 0.011</td>
<td></td>
</tr>
<tr>
<td>Total Effect</td>
<td>0.040</td>
<td>0.019 to 0.062</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

- Partnership status patterns are associated with biomarkers in mid adulthood
- The observed effects differed between men and women implying that the mechanisms that link partnership status and health may be gender specific
- In men, those that never married or cohabited had significantly higher levels on three haemostatic function biomarkers as well as worse respiratory function compared to men that were married and remained married for the duration of the observation period
Conclusion - II

- In women those that married in mid/late 20’s or early 30’s and remained married for the whole observation period had the best health
- Women that never married or cohabited had worse health compared to married women
- However, this effect was only manifested in fibrinogen levels, indicating that not marrying or cohabiting is less detrimental in women compared to men or that being married appears to be more beneficial to men
Conclusion - III

- We found that with the exception of worse respiratory function in men, non-marital cohabitation has similar effects to being married on mid-life health.
- Not married cohabiters of both genders did not differ from married participants in the biomarkers used in our study.
- For both genders transitions from and to marriage or non-marital cohabitation do not have a detrimental effect on mid-life health.
- Smoking partly mediates the association between partnership status and fibrinogen.
Limitations

- Despite the wealth of the 1958 cohort, bias due to unknown unmeasured confounders cannot be ruled out, although sensitivity analysis where potential confounders were simulated supported our results.

- The longitudinal typology captured the cumulative effect over 21 years of trajectories of partnership status in biomarkers in mid-life. Investigation of the short term effects of events such as marital dissolution was not possible with this approach.

- Data on partnership status were based on self-reports. Although the latent variable specification of our longitudinal typology controls for measurement error, extreme bias (a participant misreporting in all nine indicators of our typology) may have influenced our results.

- Our results can only be generalised to those born in 1958 and perhaps to other cohorts born close to this year.
Suggestions

- Life course studies are methodologically challenging
- However, solutions with reasonable assumptions exist
- Directed Acyclic Graphs (DAGs) are very useful for life course studies
• DAGs should be used to express realistically complex hypotheses
• This will help us isolate the effect(s) of interest and choose the most appropriate model(s) and assumptions
• Isolate and reliably quantify policy modifiable effects
• Not always straightforward, but doable
Thank you for your attention