**Life course biological trajectories: maximising the value of longitudinal studies**

**Rebecca Hardy, Dara O'Neill**

CLOSER

University College London

London

UK

Phone: +44(0)20 7612 6023

Email: rebecca.hardy@ucl.ac.uk

Establishing how markers of biological function and structure change across life, identifying 'normal' or 'healthy' age-related trajectories, and discerning the life course factors associated with deviation in these trajectories, are key to understanding the development of impairment and disease. The study of change emphasises the pivotal role in research of longitudinal data, since trajectories inferred from multiple cross-sectional studies may be influenced by secular or cohort differences. However, even for a measurement as apparently common as blood pressure (BP), no study yet has measured this across the entire life course in the same sample of individuals. One investigation that modelled systolic BP from seven UK prospective cohort studies, each covering different but overlapping periods of the life course from ages 7 to 80+ years (Wills et al. 2011), demonstrated that although development in childhood (in more recently born cohorts) and later life decline (in earlier born cohorts) has been better characterised, modelling trajectories in early adulthood and midlife is hindered by more limited availability of data.

The benefits of using multiple studies for understanding life course trajectories are becoming increasingly apparent. Replicability of findings from one study can be evaluated in another, while combining data from multiple studies increases statistical power and improves the precision of estimates in meta- or pooled analyses. Differences in findings across time and place can reveal important mechanisms, such as how lifestyle influences BP changes in midlife (Gurven et al. 2012), and different confounding structures can be used to provide evidence of causality (Brion et al. 2011). In order to make valid comparisons between studies that were not necessarily set up to be comparable is however challenging and time-consuming; careful harmonisation of measures, samples and analytical procedures are required.

A recognition of the importance of harmonisation has informed our efforts at the Cohort and Longitudinal Studies Enhancement Resources (CLOSER) consortium to maximise the use, value and impact of longitudinal research (O'Neill et al. 2019). CLOSER's work

packages have produced retrospectively harmonised datasets and cross-study resource guides that can help researchers leverage existing longitudinal data to answer new questions about changes in health and its determinants over the life course. For example, one CLOSER harmonisation project studied the rise of the obesity epidemic in the UK by age and birth cohort. Johnson et al. (2015) harmonised repeat measures of body size from five British birth cohort studies born in 1946, 1958, 1970, 1990–92 and 2001, and then showed that the probability of being overweight/obese by age 11 in the two younger cohorts was around double that of the older cohorts. Additionally, across the three older cohorts, a downward trend in age at which the median adult became overweight illustrated how more recent cohorts areaccumulating longer periods of life overweight or obese. The harmonised dataset has been reused in analyses presented in this issue illustrating how the Benn parameter has changed across the cohorts (Johnson et al. 2020). The dataset has also been linked with harmonised data on occupational social class to illustrate how social inequalities in body mass index (BMI) have emerged in parallel with the obesity epidemic and have since persisted (Bann et al. 2018).

When dealing with longitudinal data which covers large portions of the life course, harmonisation is also required within studies. The ideal of using identical measurement procedures at every time point within a study is not always feasible. The way some aspects of function are measured may, by necessity, change with age, such as cognitive testing during childhood. In addition, continuing developments in technology mean that new, improved and more convenient instruments for measuring the same characteristics are introduced. Comparison of instruments is required in order to ensure validity of conclusions from evaluations of mean levels of change within and between studies. It has been demonstrated, in a longitudinal analysis of BP, that rates of change would be overestimated without use of conversion equations to account for a switch within studies from manual sphygmanomometers to automated devices (Wills et al. 2011). In response to such challenges, CLOSER carried out a machine comparison trial on devices commonly used in longitudinal studies for measuring BP, grip strength, and lung

function.

Standardisation of methods of data collection across studies would allow for more valid cross-study comparisons. The work undertaken on retrospective harmonisation can potentially provide evidence on which to base future measurement decisions and encourage greater prospectively harmonised measurement across studies. However, there is a concurrent need to support innovation and to be adaptive to unique characteristics of different studies. The value of some measures may only become apparent much later in the lifetime of a study, and thus variation in measures collected maximises the possibilities of future scientific discovery. On-going multi-measure calibration may be a solution to achieving the within- and between-study comparability required for trajectory research while accounting for the diverse needs of individual studies. The creation of calibrated question banks could enable progress, but doing so is not without challenges, both in terms of resourcing and coordination. CLOSER's 'Discovery' meta-data enhancement platform, was developed to improve access to details about question usage and data availability across and within studies. CLOSER Discovery is built on standardised and interoperable technology, and this is key to achieving compatability with similar platforms used by other studies and realising the opportunties such platforms can jointly offer.

In addition to the need for improved discoverability and harmonisation of data for identifying and evaluating trajectories, researchers need the skills in order to perform complex analytic work. The arrival of new software tools have brought the possibilities of advanced trajectory modelling to more researchers than ever before, but increased accessibility does not in itself ensure better analysis. As software packages emerge allowing more complex analysis (such as non-linear trajectories, episodic disease occurrences, and missing data imputation), the importance of building sufficient analytic competencies become ever more pressing. CLOSER's training and capacity building efforts are helping to develop and extend expertise in effectively and appropriately

leveraging longitudinal study data to further understanding of how health and its determinants develop across the life course. New innovations in measurement, such as the use of wearable devices, will only increase complexity. While historically studies have attempted to capture a 'normal' or 'average' level of function at any given age, there is increasing interest in the implications of variability and short-term fluctuations in function.

As a consortium, we recognise that collaboration across the research community and across disciplines is the basis on which to fulfill the research potential of longitudinal studies to further knowledge of biological change across the life course, to collectively build best practice and to ensure that the new insights identified by researchers have maximal impact.

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