RESEARCH SUMMARY

Impact of early personal-history characteristics on the Pace of Ageing: implications for clinical trials of therapies to slow aging and expand healthspan. Belsky, D.W., Caspi, A., Cohen, H.J., Kraus, W.E., Ramrakha, S., Poulton, R. & Mofitt, T.E. (2017)
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This paper follows on from that of Caspi *et al* (2016) in that it takes the analysis of data from the New Zealand Dunedin longitudinal birth cohort 1972-1973. The Caspi *et al* paper showed that in the birth cohort, 38 years on, around 20% of the adults were associated with a disproportionate amount of healthcare and social costs; the remarkable finding was that the costly fraction of the cohort showed significantly poor brain health by the age of 3 compared to the rest. In the current paper, children from the cohort with poor childhood characteristics showed a faster pace of ageing in the period of 26-38 years. This review is limited to the early personal-history characteristics on the Pace of Ageing; I will not review the future therapeutic possibilities that might lead to a slowing of the aging process.

Ageing Markers. The rate of ageing was measured by changes to 18 biomarkers at the ages of 26, 32 and 38 years. The biomarkers were: apolipoprotein B100/A1 ratio (a risk marker for myocardial infarction), mean arterial blood pressure (a marker for hypertension), body mass index and waist/hip ratio (both are risk markers for obesity), C-reactive protein (CRP is an inflammatory marker), white blood cell count (markers for infection and leukaemia), cardio-respiratory fitness, creatinine clearance (a marker for kidney function), forced respiratory volume in 1 second and forced respiratory vital capacity ratio (both are markers for lung function), glycated haemoglobin (a marker for diabetes), high-density lipoprotein (a marker for atherosclerosis), lipoprotein(a), leukocyte telomere length (a marker for genomic instability), periodontal disease (a maker for inflammation), total cholesterol (a marker for cardiovascular disease), triglycerides (a marker for metabolic syndrome), and urea nitrogen (a renal function marker). It should be noted that all the biomarkers, whether physiological or biochemical, can be measured precisely.

Normalizing the Change in Markers. The rates of change of the biomarkers values were scaled to a single index in years (a statistical normalization process) so that the average member of the cohort had a pace of ageing to 1 year of physiological change for 1 chronological year. The scaled data for the pace of ageing showed a normal distribution with a mean of 1 and a standard distribution (SD) of 0.38. The distribution was then divided into 3 groups: a slow-ageing group comprised 25% of the population with a pace of ageing <1 SD (<35 years), a normal-ageing group in the range of ±1 SD (50% of the population) (35-41 years), and a fast-ageing group comprised of 25% of the population with a pace of ageing >1 SD (>41 years).
To put these values of the pace of ageing into an easily understandable form, the slow-ageing group are ageing at <62.5% of the mean of the normal group, and the

fast-ageing group are aging at >62.5% of the mean of the normal group. What causes these differences in the pace of ageing signified by the change in biomarkers?

Effect of Childhood Histories within the Cohort. The Dunedin Birth Cohort contains detailed personal childhood histories for each member. Only those histories where the regression line through the data has a regression coefficient r that is significantly different from zero are remarked on in this review and are show in table 1.[1]

Table 1. Childhood characteristic risk factors affecting the pace of ageing from 26 to 38 years.

Childhood characteristic	Lower value	Upper value	Coefficient *r*	Age for data collection
Social class	Low	High	-0.17	0 - 15 year period
Adverse experience	None	4+	0.14	3 – 15 year period
Health	Poor	Excellent	-0.10	3 – 11 year period
IQ	60	140	-0.19	7, 9, 11, 13 (averaged)
Self control	-3	1	-0.23	3, 5, 7, 9 (averaged)

One other risk factor was the age of the longest-lived grandparent; range 60 – 100 years, r = -0.12.
In order to get a simple description of the effect of risk factors on the health changes of the fast pace of ageing group, compared with the group showing average pace of ageing, each risk factor was quantified to a cut-off point as a risk. The straightforward example would be having no grand parent who survived beyond 80 years; that would be one risk factor. The other 5 risk factor cut-off points are more complicated and can be found in the Supplementary Information to the paper.

Table 2 compares the percentage of subjects in the cohort with 0, 1, and 2 or more cumulative risk factors in the groups for the average pace of ageing and for the group with fast pace of ageing. The comparison is then extended to two subsets of the cohort: the subset with a recent prescription fill (the issue of a doctor's prescription for medication), and a group that had a non-pregnancy related recent hospital admission.
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Table 2. Comparison of risk factors on the population (%) in subsets of the pace of ageing groups.

	Average pace of ageing			Fast pace of ageing		
Subset	**No risk**	**1 risk**	**2+ risks**	**No risk**	**1 risk**	**2+ risks**
Full cohort	47%	33%	20%	31%	28%	41%
Prescription fill	45%	32%	23%	30%	26%	43%
Hospital admission	40%	31%	29%	28%	14%	58%

[1] A regression line is a statistically drawn line through a scatter of data points to give the best fit; the coefficient r is a measure of the slope. This enables the user to determine if the slope differs significantly from zero – a flat line with no slope. All the regression coefficients in table 1 are significantly different from zero; thus showing that there is a true relationship between the pace of ageing and the childhood risk characteristic.

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The clear difference between the average and fast ageing groups is a doubling of the percentage of subjects with 2 or more risks in the fast ageing group. This is mirrored in the increase in prescription fills and hospital admission.

Summary. This paper has shown that risk factors in childhood development and childhood experiences are associated with a faster pace of ageing, compared with average ageing in the cohort. The presence of two or more risks doubles the pace of ageing. The increase in the number of prescription fills, and hospital admission rates, at 38 years is a warning for future increases in health and social care costs of the fast-ageing group. This paper, taken together with its predecessor Caspi *et al* (2016), is a stark reminder about the need for society to get its Early Years Policies right in order to reduce the childhood risk factors and future costs of health and social care.

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