Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Biomarkers of ageing in New Zealand VLBW young adults and controls

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BACKGROUND: There is individual variation in physiological ageing. Former very low birthweight (VLBW; birthweight < 1500 g) young adults may have less satisfactory measurements on some physiological parameters than term controls. We hypothesized that a summation score of physiological biomarkers that change with age would show VLBW adults to have a more advanced physiologic age than controls.

METHODS: VLBW adults (229; 71% survivors of a national VLBW cohort) and term-born controls (100) were clinically assessed at 26–30 years. Ten measured physiological biomarkers were selected and measurements converted to *z*-scores using normative reference data. Between-group comparisons were tested for statistical significance for individual biomarker *z*-scores and a summation score.

RESULTS: Nine of 10 biomarkers showed a mean *z*-score suggestive of older physiological age in the VLBW group versus controls. The observed mean difference in the summation score was highly significant ($p < 0.001$), representing a mean shift of 0.47 SD in the distribution of test scores for VLBW relative to controls.

CONCLUSIONS: Utilizing a 10-biomarker score, VLBW young adults have a score indicative of poorer physiological functioning than term-born controls. Repeating these measures after an interval could provide insights into the comparative pace of ageing between VLBW and term-born adults.

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IMPACT:

- A summation score of 10 physiological biomarkers that are known to change with age shows that former very low birthweight adults have significantly poorer physiological functioning by the end of their third decade than term-born controls.
- This result adds to existing literature showing very preterm and very low birthweight young adults often have physiological and metabolic test results that are less satisfactory than those from term controls, despite mostly being in the normal range for age; for instance, higher systolic blood pressure.
- Although the pace of ageing in later years is yet to be established, the implications of this study are that preventative measures and lifestyle choices that impact on physiological ageing might have even greater importance for very preterm and very low birthweight graduates.

INTRODUCTION

The process of ageing, that is, the body's functional and structural decline, occurs at different rates in different individuals.[1,2] Recently, a number of studies have attempted to quantify a biological age that can be used to either predict mortality[2,3] or to identify individuals who, although free of age-related disease, are physiologically more advanced than their chronological age.[4]

Very low birthweight (VLBW; <1500 g birthweight) and very preterm (VP; <32 weeks gestation) infants account ~2% of births in developed countries.[5] While there is an extensive literature documenting increased rates of poor growth, physical health problems and neurodevelopmental impairments among VLBW/VP graduates during childhood, it is only more recently that such individuals have been followed to adulthood. Data from Scandinavian population registries show that preterm birth (<37 weeks) is associated with increased mortality in young adulthood; the strongest associations being with congenital anomalies, respiratory, endocrine and cardiovascular disorders.[6] Several longitudinal population-based studies have reported that while most VLBW/VP young adults are healthy, compared with controls they are more likely to have significant respiratory airflow obstruction, raised systolic blood pressure and markers of the metabolic syndrome.[7–9] Other longitudinal studies have documented cardiac and renal changes, including reduced left ventricular volumes and smaller kidney size.[10] As a result, the VLBW/VP young adult phenotype has been characterized as being

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at risk for the early onset of chronic diseases[11] or "premature ageing".[12]

The New Zealand 1986 VLBW Follow-Up Study is a longitudinal study of all VLBW infants live born in New Zealand in 1986 and admitted to an intensive care unit.[13] At age 26–30 years, 229 members of the cohort (71% survivors) and 100 term-born controls came to one centre for 2 days of medical and neurocognitive assessments (cohort flow diagram, Supplementary Fig. 1 (online)). We hypothesized that, as represented by a summation score of physiological biomarkers that are known to change with age, the VLBW cohort compared with term-born controls would on average have a higher score, indicative of a physiological age that was more advanced than that of term-born controls.

METHODS

The NZ 1986 VLBW Study protocol[13] and methods[14] have been published. We selected 10 biomarkers, which had been included in our assessment protocol, that are known to change in value associated with the ageing of organ systems and have been used to calculate biological age in other studies[2,4] (Table 1; Supplementary Table 1 (online)).

A venipuncture was obtained after an overnight fast, an aliquot rapidly separated and the plasma samples stored at −80 °C for assay within 6 months of receipt. Laboratory measurements were undertaken by the Canterbury Health Laboratories (CHL), which is accredited with International Accreditation New Zealand for all medical testing procedures. Glycated haemoglobin (Hb) was measured using a cation exchange high-performance liquid chromatography automated testing system (Bio-Rad D100: Bio-Rad Laboratories Pty, Auckland, New Zealand), standardized through traceability to the IFCC (International Federation of Clinical Chemistry) reference method, with results reported as mmol/mol. Fasting insulin (pmol/L) was assayed on a Roche Cobas e411 analyser (Roche Diagnostics NZ, Auckland, New Zealand) after polyethylene glycol precipitation of immunoglobulins. Plasma triglycerides, total cholesterol and serum creatinine were determined by the Architect c8000 analyser (Abbott Laboratories, Wellington, New Zealand). Blood pressure (the third of three readings recorded within a 15-min period of resting) was measured manually by trained health professionals using a mercury sphygmomanometer with a large cuff for arm circumference >33 cm in the participants' non-dominant arm while individuals were seated. Endothelial function (reactive hyperaemic index: RHI) was measured by peripheral arterial tonometry (EndoPAT).[15] Forced expiratory volume in 1 s (FEV_1) was measured according to ATS/ERS specifications.[16] Waist-to-hip ratio (WHR) was calculated from waist circumference measured at the narrowest point between the lower costal border and the top of the iliac crest, and hip circumference measured at the widest part of buttocks or hip.[17] For periodontal attachment loss, survey participants were examined in a dental clinic following the protocol used in the 2009 New Zealand oral health survey (https://www.health.govt.nz/publication/our-oral-health-key-findings-2009-new-zealand-oral-health-survey). Dental examiners, who were blinded to participant group, used an intra-oral mirror and a periodontal probe for examination of periodontal tissue for destruction (pocket depth and gingival recession). The severity of periodontal disease was calculated [from gingival recession + periodontal pocket depth (in mm)] to produce a clinical attachment loss (CAL) score.

For each biomarker, the *z*-score was calculated from published age appropriate reference data (total cholesterol, triglycerides, systolic blood pressure (BP), RHI), from CHL data (glycated Hb, fasting insulin, creatinine), using an online programme (FEV_1) or from the control group mean and standard deviation data (WHR, periodontal CAL score). Gender-specific reference norms were used for all biomarkers, except glycated Hb and RHI. Cholesterol and triglyceride reference data were from the US National Health and Nutrition Examination Survey (NHANES III) 1993 published data for white 25–34-year-old subjects.[18] Systolic BP reference data were from 26-year-old New Zealand subjects included in the Dunedin Multidisciplinary Health and Development Study, who had nearly all been born at term.[19] FEV_1 reference data were from the Global Lung Function Initiative 2012 data[20] and using an online programme that accounts for individual age, height, sex and ethnicity (http://gligastransfer.org.au/calcs/spiro.html). RHI reference data were from healthy, non-smoking Norwegian volunteers aged 20–50 years following cuff occlusion for 5 min, as in our protocol.[21] Glycated Hb, fasting insulin and creatinine reference data were based on CHL routine analysis of blood tests from 20- to 39-year-old subjects. Glycated Hb reference data were from blood tests over a 2-year period and fasting insulin from blood tests over an 8-year period, excluding known diabetic patients and those investigated for hypoglycaemia. Serum creatinine reference data were from blood tests over a 12-month period from subjects who were not cared for in the intensive care unit and for whom renal function tests were not specifically indicated (known or suspected renal disease/impairment). Glycated Hb, fasting insulin and serum creatinine data were further refined using the procedures described by Horn et al.[22] to exclude outliers.

For biomarkers that decline with age (FEV_1 and RHI) plus and minus *z*-scores were reversed prior to deriving the novel summation score by simple addition of the *z*-scores.

Table 1. Biomarkers used to calculate a summation score reflective of physiological age and normative reference data.

Biomarker	Reference data source (see text)	Normative reference means (SD)
Glycated Hb	CHL	32.01 ± 4.76 mmol/mol
Fasting insulin	CHL	M 86.30 ± 72.52 pmol/L F 83.01 ± 68.39 pmol/L
Triglycerides	NHANES III	M 1.40 ± 1.80 mmol/L F 1.15 ± 1.58 mmol/L
Total cholesterol	NHANES III	M 5.15 ± 1.20 mmol/L F 4.97 ± 1.27 mmol/L
Creatinine	CHL	M 88.90 ± 11.21 μmol/L F 73.30 ± 9.83 μmol/L
Systolic BP	DMHDS	M 121.6 ± 10.31 mmHg F 111.4 ± 8.99 mmHg
RHI (EndoPAT)	Faizi et al.[21]	1.88 ± 0.53
FEV_1	GLI	*z*-Score from GLI online calculator based on age, height, sex, ethnicity[a]
Waist–hip ratio	Control group mean and SD	M 0.859 ± 0.063 F 0.797 ± 0.062
Periodontal disease CAL score	Control group mean and SD	M 4.11 ± 1.43 mm F 4.18 ± 1.36 mm

RHI endothelial function (reactive hyperaemic index),[15] *FEV_1* forced expiratory volume in 1 s, *BP* blood pressure, *CAL* clinical attachment loss, *CHL* Canterbury Health Laboratories (see text), *NHANES III* The US National Health and Nutrition Examination Survey,[18] *DMHDS* Dunedin Multidisciplinary Health and Development Study,[19] *GLI* Global Lung Function Initiative.[19]
[a]http://gligastransfer.org.au/calcs/spiro.html (accessed 14 Aug 2019).

Data analysis and statistics

Statistical comparisons between VLBW and controls were conducted using either the χ^2 test of independence or

independent-samples *t* test, with kernel density graphs used to compare the distributions of individual biomarker *z*-scores and the total summation index in each group. We carried out two sensitivity analyses, first, excluding participants with known diagnoses and those with extreme *z*-scores (>4) on individual biomarkers; second, using multiple linear regression methods to adjust the observed mean differences between groups for (a) perinatal and demographic factors (assessment age, gender, ethnicity, birth order, parental education, socioeconomic status family of origin, maternal age at child birth, maternal smoking in pregnancy, breastfeeding), and (b) adult education and lifestyle factors (participant education level, caffeine consumption, tobacco use, alcohol use, illicit drug use, frequency of exercise) in addition to perinatal and demographic factors. Statistical analyses were conducted using SAS 9.4 and graphs were constructed using Stata 15.

Not all biomarkers were assessed on all participants, although missing values were few (Supplementary Table 2 (online)). With these sample sizes, the study had 80% power at $\alpha = 0.05$ to detect mean differences between groups in the range from 0.34 to 0.36 SD.[23]

The study was approved by the Upper South B Regional Ethics Committee, New Zealand, and written informed consent was given by all participants.

The study was registered with the Australian Clinical Trials Registry: ACTRN12612000995875.

RESULTS

The perinatal and demographic characteristics of the VLBW and control participants are shown in Table 2.

Table 3 shows the mean scaled *z*-score differences between VLBW and control groups (with actual mean (SD) values shown in Supplementary Table 2 (online)). All comparisons, with the exception of creatinine, show VLBW to have higher unadjusted mean scores than controls, although the differences are statistically significant only for systolic BP, FEV_1 and endothelial function. The observed mean difference in total scores, 1.73 (95% confidence interval (CI): 0.82, 2.64), was highly significant ($p < 0.001$) and represents a mean shift of 0.47 SD in the distribution of test scores for VLBW relative to the controls. This, in turn, equates to a "moderate" effect as described by Cohen.[23]

Three measures, systolic BP, RHI and FEV_1, contributed substantially to the total composite *z*-score difference between groups. If any of these three measures was removed from the total score, the difference between the two groups was attenuated (but remained statistically significant). If all three were removed, then the total *z*-score difference between the groups reduced to 0.62 (95% CI: −1.10, 1.32), $p = 0.09$. The difference was still consistent with poorer overall functioning among VLBW than controls, but was statistically non-significant.

Supplementary Table 3 (online) shows the mean *z*-scores differences between VLBW and control groups (a) excluding participants with a known diagnosis of diabetes (1 VLBW, 3 control) or hypertension (5 VLBW), and (b) excluding those with known diagnoses together with outlier *z*-scores > 4). The conclusions are unaltered, but the latter exclusions increase the overall mean difference with an effect size difference of 0.55 SD between the groups.

Supplementary Table 4 (online) shows *z*-score differences between the VLBW and control groups adjusted for (a) perinatal and demographic factors and (b) for adult education and lifestyle factors. The former adjustment results in the overall effect size difference in total scores to reduce to 0.42 SD and the latter to 0.36 SD.

Figure 1 shows the distribution of the sum of *z*-scores for the VLBW and control groups and Fig. 2 shows graphs that summarize the full distributional differences for each measure, again showing consistent shifts to the right for VLBW group for all parameters with the exception of creatinine.

Table 2. Perinatal and demographic characteristics of VLBW and control groups.

Measure	VLBW ($N = 229$)	Controls ($N = 100$)	*P* value[a]
Mean (SD) age at assessment	28.5 (1.1)	28.3 (0.9)	0.13
Male, % (*n*)	44.5 (102)	36.0 (36)	0.15
Māori/Pacific Island, % (*n*)	31.0 (71)	21.0 (21)	0.06
Mean (SD) birthweight (g)	1133 (237)	3372 (565)	<0.001
<1000 g, % (*n*)	28.0 (64)		
Mean (SD) gestation (weeks)	29.2 (2.5)		
<28 weeks gestation, % (*n*)	24.9 (57)		
SGA, % (*n*)	31.4 (72)		
RDS, % (*n*)	54.6 (125)		
BPD, % (*n*)	20.1 (46)		
ANS, % (*n*)	56.3 (129)		
ROP, % (*n*)	19.7 (45)		
Any neurosensory disability (age 7–8 years), % (*n*)[b]	23.0 (51)		
Mod/severe disability (age 7–8 years), % (*n*)[b]	5.9 (13)		

SGA small for gestational age (birthweight <10% centile), *RDS* respiratory distress syndrome, *BPD* bronchopulmonary dysplasia (oxygen requirement at 36 weeks post-menstrual age), *ANS* antenatal corticosteroids, *ROP* retinopathy of prematurity.
[a]Comparisons of VLBW and controls by *t* test or χ^2.
[b]Seven of the VLBW cohort were not assessed for neurosensory disability at age 7–8 years. Moderate or severe disability at 7–8 years of age was defined as cerebral palsy in non-ambulant children or in ambulant children causing considerable limitation of movement, or bilateral sensorineural deafness requiring hearing aids, or bilateral blindness, or an IQ score of >2 SD below the test mean (<70) on the Revised Wechsler Intelligence Scale for Children (WISC-R).[13]

DISCUSSION

To compare the relative physiological ages of a national population-based cohort of VLBW young adults compared with same aged term-born controls, we have arbitrarily derived a novel composite score using ten easily measured biomarkers known to consistently increase or decrease with age. Nine of the 10 biomarkers showed a mean *z*-score suggestive of older physiological age in the VLBW cohort compared with controls, although the difference was only significant for three individual biomarkers. The observed mean difference in total scores was highly significant ($p < 0.001$), representing a mean shift of 0.47 SD in the distribution of test scores for VLBW relative to the controls.

A life-course approach recognizes that many physiological functions reach a peak at around the third decade of life, followed by a subsequent decline.[24] Determinants of peak structure and function include baseline genetic variation modified by key exposures during critical windows of development, as well as broader social and environmental factors.[25] Equally, the rate of decline from peak function will be influenced by many factors, including socioeconomic status and lifestyle choices. There is now strong evidence that the potential peak structure and function of many organs may be reduced by very premature birth, both from perturbations in organ growth and development, and also iatrogenic harm as a result of the necessary neonatal intensive

Table 3. Mean scaled *z*-score differences for 10 biomarkers and the total sum of *z*-scores between VLBW and control groups.

Z-score measure	VLBW mean (SD)	Control mean (SD)	Unadjusted mean difference (95% CI)	*P* value
Glycated Hb	−0.02 (0.93)	−0.18 (1.29)	0.163 (−0.086, 0.412)	0.20
Fasting insulin	−0.16 (0.80)	−0.27 (0.49)	0.111 (−0.061, 0.283)	0.21
Triglycerides	−0.01 (0.39)	−0.08 (0.41)	0.071 (−0.022, 0.164)	0.14
Cholesterol	−0.36 (0.67)	−0.36 (0.87)	0.002 (−0.172, 0.176)	0.98
Creatinine	0.38 (0.80)	0.44 (0.80)	−0.061 (−0.251, 0.129)	0.53
Systolic BP	−0.22 (1.19)	−0.63 (1.03)	0.399 (0.130, 0.667)	0.004
RHI (EndoPAT)	−0.05 (1.08)	−0.39 (1.33)	0.344 (0.060, 0.628)	0.018
FEV_1	0.67 (1.20)	0.13 (1.17)	0.544 (0.263, 0.825)	0.000
Waist–hip ratio	0.23 (1.28)	0.00 (0.99)	0.229 (−0.053, 0.511)	0.11
Periodontal disease (maximum attachment loss)	0.14 (0.98)	0.00 (1.00)	0.145 (−0.088, 0.378)	0.22
Total score[a]	0.31 (3.80)	−1.42 (3.36)	1.729 (0.820, 2.637)	0.000

RHI endothelial function [reactive hyperaemic index], *FEV_1* forced expiratory volume in 1 s, *BP* blood pressure.
[a]The total score mean does not equal the sum of the means of the individual measures due to slight variations in the sample sizes assessed on each measure. Total score based on 190 VLBW and 93 controls.

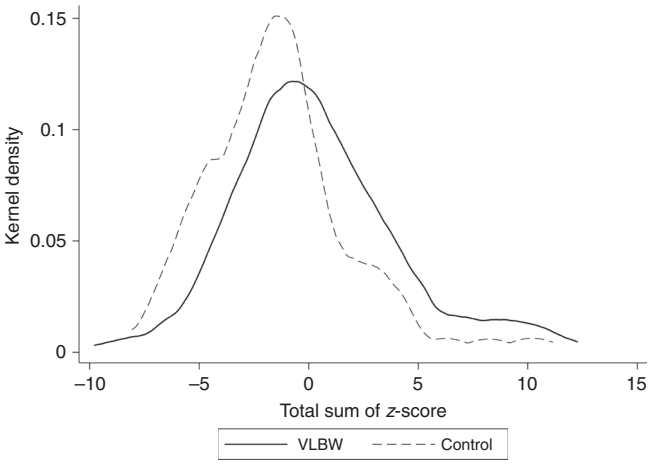

Fig. 1 The distribution of the sum of biomarker *z*-scores for the VLBW and control groups.

care.[26,27] Current studies show that by early adulthood, while most physiological and metabolic parameters fall within the normal range for age, VP/VLBW graduates on average have results on the less satisfactory side of the ledger, for example, higher systolic BP or lower FEV_1,[8,9] as in this cohort[14] (Supplementary Table 2 (online)). To date, however, there is a lack of information in this group about the rate of decline from peak function, often termed the pace of ageing.

Moffitt et al.[28] have listed six research imperatives to advance knowledge of the pace of ageing. These include identifying better biomarkers of physiological age and the most efficient "short-form" score, and determining what factors correlate with the pace of ageing in young adults; both of which we have addressed in this study. The 10 biomarkers selected were all easy to assess and inexpensive and could constitute a "short-form" score that is readily repeatable at intervals. Periodontal attachment loss was included because epidemiological data from the NHANES III study[29] and elsewhere[30] show the prevalence, extent and severity of gingival recession increases with age, and a standard protocol to assess this that had been widely used in the 2009 New Zealand National Oral Health Survey was available.[31] The Adults Born Preterm Infant Collaborative (APIC) group, an international collaboration of mostly population-based studies of VP/VLBW adults from high income countries, has recently made recommendations on "common-core" assessment measures for use in VP/VLBW adult follow-up studies (Kajantie E, personal communication, 16th Feb 2020). As APIC collaborators we will explore whether our findings can be replicated and validated in other populations. The APIC group would be well placed to achieve consensus on a "short-form" biomarker score that could be used in studies of ageing of preterm adults, that is, repeating the score after an interval of several years.[4]

Several studies have assessed different combinations of biomarkers in adulthood for the prediction of later morbidity and mortality.[3,32] Most included adults older than 40 years. Levine[2] estimated biological age from algorithms based on ten biomarkers in over 9000 individuals aged 30–75 years in the NHANES project (Supplementary Table 1 (online)). Systolic BP and FEV_1 had the highest correlations with chronological age ($r > 0.50$) with three other measures used in our study, serum total cholesterol, glycated Hb and serum creatinine, also highly correlated. Over an 18-year period, the algorithm for biological age was a more reliable predictor of mortality than chronological age.[2]

Belsky et al.[4] assessed the "biological age" of 38-year-old participants ($n = 954$) in the Dunedin Multidisciplinary Health and Development Study using the 10 biomarkers and algorithm previously used in the NHANES study,[3] and the reported biological age was normally distributed (mean 38 years; SD 3.23). These researchers also assessed the pace of ageing in their cohort using 18 biomarkers measured at ages 26 and 38 years (Supplementary Table 1 (online)). The pace of ageing varied from close to zero, to nearly 3 years per chronological year.[4] In addition, more advanced biological age at 38 years was significantly correlated with both poorer subjective and objective physical functioning, and with poorer cognitive function.[4] We have assessed measures of physical and neurocognitive functioning in both VLBW and control groups, and plan to repeat these assessments together with physiological biomarkers in a further 10 years to evaluate the pace of ageing in our cohort.

Würtz et al.[33] investigated metabolic signatures, derived from 87 circulating metabolic measures, associated with birthweight in over 18,000 Finnish individuals with an average age 26 years (range 15–75). These researchers reported that lower birthweight, adjusted for GA, was adversely associated with a range of cardiometabolic and inflammatory biomarkers, but that the strength of the associations were weak and roughly equivalent to that resulting from a higher body mass index (BMI). We opted for WHR rather than BMI because, while both are measures of obesity and are recognized as risk factors for cardiovascular and other diseases, WHR is a more specific indicator of abdominal fat distribution. In a longitudinal Australian study of 9000 adults aged 20–69 years, WHR was a

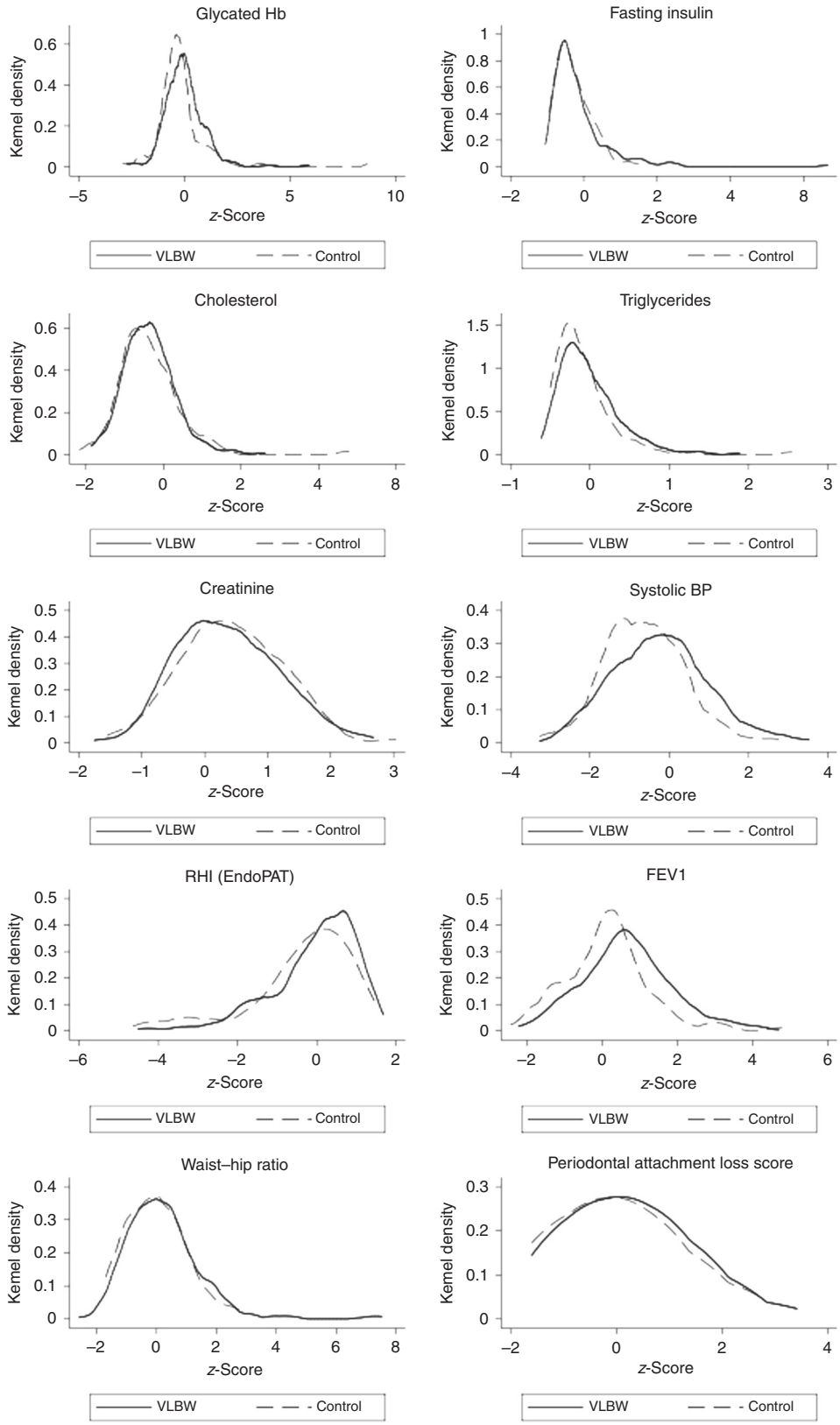

Fig. 2 The distribution of biomarker *z*-scores in VLBW and Control groups. Each panel shows the distribution for one biomarker, from the top left these are glycated haemoglobin (Hb), fasting insulin, cholesterol, triglycerides, creatinine, systolic blood pressure (BP), reactive hyperaemic index (RHI), forced expiratory volume in 1 s (FEV1), waist-to-hip ratio, periodontal attachment loss score.

stronger predictor of all-cause and cardiovascular disease mortality than BMI and other anthropometric measures of obesity.[34] Telomere length, and specifically leucocyte telomere length (LTL) has been proposed as a marker of biological ageing, but, as noted in a recent extensive review,[35] while shorter LTL is associated with older age, there are a number of methodological issues regarding measurement and both epidemiological and clinical studies investigating the value of shortening of LTL as a biomarker of ageing have produced equivocal results.

In addition to the readily assessable biomarkers we have studied, further strengths of our study include that this is a national population-based cohort with a high (71%) retention rate. Weaknesses include that we have arbitrarily derived a summary score indicative of physiological age by totalling *z*-scores for 10 biomarkers that requires validation in other cohorts. This score assumes each biomarker has equal weight, although the three biomarkers (systolic BP, RHI and FEV_1) contribute disproportionally to the total composite score. The literature on weighting linear score composites, however, suggests equal weighting produces scores that have greater robustness than weighted scores. This is because weights will often be sample or context specific, and will not necessarily generalize to other samples in other contexts.[36]

The NHANES III 1993 data on cholesterol and triglycerides were obtained in 1976–1980 in a North American population that might not be representative of New Zealand in 2013–2016. The CHL-derived data, despite being a very large dataset, did all come from medical referrals even though those with specific clinical problems that might affect the results, together with outliers, were excluded. Where we used the control group to generate "normative" data, we were necessarily constrained by small numbers. Although nearly one-third of the VLBW cohort identified their ethnicity as Maori or Pacific Islander, the numbers were insufficient to assess data by different ethnicities. Despite these issues, the direction of difference between the groups was consistent across all measures and the summation score was highly significantly different. The observed differences persisted and remained consistent when adjusted for perinatal/demographic factors and for adult education and lifestyle factors.

In conclusion, utilizing a novel summation score of 10 biomarkers, we have shown that VLBW young adults have overall scores indicative of poorer physiological functioning than term-born controls. Repeating these measures after an interval could provide insights into the comparative pace of ageing between VLBW graduates and controls.

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AUTHOR CONTRIBUTIONS

Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data: B.A.D., J.H., B.D. V.A.M.K., J.M.E., J.Y. and R.J.M. Drafting the article or revising it critically for important intellectual content: B.A.D., J.H., S.L.H. Final approval of the version to be published: All authors.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-020-0882-x) contains supplementary material, which is available to authorized users.

Competing interests: The authors declare no competing interests.

Patient consent: The study was approved by the Upper South B Regional Ethics Committee, New Zealand, and written informed consent was given by all participants.

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