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Low Birth Weight in MZ Twins Discordant for Birth Weight is Associated with Shorter Telomere Length and lower IQ, but not Anxiety/Depression in Later Life

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Shorter telomere length (TL) has found to be associated with lower birth weight and with lower cognitive ability and psychiatric disorders. However, the direction of causation of these associations and the extent to which they are genetically or environmentally mediated are unclear. Within-pair comparisons of monozygotic (MZ) and dizygotic (DZ) twins can throw light on these questions. We investigated correlations of within pair differences in telomere length, IQ, and anxiety/depression in an initial sample from Brisbane (242 MZ pairs, 245 DZ same sex (DZSS) pairs) and in replication samples from Amsterdam (514 MZ pairs, 233 DZSS pairs) and Melbourne (19 pairs selected for extreme high or low birth weight difference). Intra-pair differences of birth weight and telomere length were significantly correlated in MZ twins, but not in DZSS twins. Greater intra-pair differences of telomere length were observed in the 10% of MZ twins with the greatest difference in birth weight compared to the bottom 90% in both samples and also in the Melbourne sample. Intra-pair differences of telomere length and IQ, but not of TL and anxiety/depression, were correlated in MZ twins, and to a smaller extent in DZSS twins. Our findings suggest that the same prenatal effects that reduce birth weight also influence telomere length in MZ twins. The association between telomere length and IQ is partly driven by the same prenatal effects that decrease birth weight.

Keywords: twins, birth weight, telomere length, IQ, anxiety/depression

Shorter telomere length has been found to be associated with cognitive deficits (Devore et al., 2011; Kingma et al., 2012; Pearce et al., 2012; Valdes et al., 2010; Yaffe et al., 2011) and with stress-related conditions, including low birth weight (Davy et al., 2009), affective psychiatric disorders (Elvsashagen et al., 2011; Hartmann et al., 2010; Hoen et al., 2011; Karabatsiakis et al., 2014; Lung et al., 2007; Simon et al., 2006; Szebeni et al., 2014; Verhoeven et al., 2014; Wikgren et al., 2012; Wolkowitz et al., 2011)

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and anxiety disorders (Hoen et al., 2013; Jergovic et al., 2014; Kananen et al., 2010; Malan et al., 2011; O'Donovan et al., 2011; Zhang et al., 2014). However, the direction of causation underlying these associations is unclear.

Telomeres are protein-bound DNA repeat structures that form the ends of linear chromosomes (de Lange, 2002) and maintain genomic stability by protecting the chromosomal termini from end-to-end recombination and chromosomes loss (Blackburn et al., 2006). They are critical in regulating cellular replicative capacity (Allsopp et al., 1992). During somatic cell replication, telomere length progressively shortens because of the inability of DNA polymerase to fully replicate the 3′ end of the DNA strand. Once a critically-short TL is reached, the cell is triggered to enter replicative senescence, which subsequently leads to cell death (Allsopp et al., 1992; Blackburn et al., 2006). The average TL of most proliferating cells (including blood leukocytes) declines substantially with age (Blackburn, 2001; Iwama et al., 1998) and shortened TL has been found to be associated with risk for age-related diseases (Benetos et al., 2004; Brouilette et al., 2007; Brouilette, et al., 2003; Fitzpatrick et al., 2007). In addition, shorter TL has been reported to be associated with a host of other conditions, including psychiatric disorders, cognitive deficits, psychological stress and low birth weight. However, whether telomere shortening actually contributes to these conditions or whether it is merely a consequence of these processes, remains unknown. A recent study showed the genomic variants that affect TL to be associated with various age-related diseases, suggesting a causal role for TL (Codd et al., 2013). TL itself is, to a large extent, heritable (Broer et al., 2013; Codd et al., 2013; Nordfjall et al., 2010; Slagboom et al., 1994).

The comparison of the associations of intra-pair differences in birth weight with intra-pair differences in TL in MZ and DZ twin pairs is a strong design to explore whether the association between traits is mediated by genetic factors or whether causality plays a role (Boomsma et al., 2005). Differences in TL and birth weight within MZ pairs are caused by non-shared environmental factors, while differences within DZ pairs are influenced by both, environmental and non-shared genetic factors. A larger intra-pair difference in birth weight within TL-discordant DZ pairs than within TL-discordant MZ pairs would thus argue for correlated genetic factors between TL and birth weight.

The first aim of the present study was therefore to assess the association between intra-pair differences for TL and birth weight in MZ and DZ pairs in a large sample from the Brisbane Longitudinal Twin Study (BLTS). Our second aim was to reassess the association between intra-pair differences in TL and IQ (intelligence quotient) and TL and anxiety/depression in the MZ and DZ pairs. We obtained replication data for TL, birth weight, and anxiety/depression (but not IQ) from a large MZ and DZ twin pair sample from the Netherlands Twin Register (NTR). As further replication, we also obtained TL measurements from a small sample of newborn MZ twins from Melbourne who were extremely discordant or concordant for birth weight.

Materials and Methods

Discovery Sample: Brisbane Longitudinal Twins Study (BLTS)

Subjects: The BLTS, which began in 1992, is an ongoing, longitudinal population-based study of melanoma risk factors and cognition and comprises adolescent Australian MZ and DZ twins and their singleton close-age siblings (Wright & Martin, 2004). Twins were enlisted by contacting the principals of primary schools in the greater Brisbane area, by media appeals, and by word of mouth. We estimate that approximately 50% of the eligible birth cohort was recruited into the study. Written, informed consent was obtained from all participants and a parent or guardian. The study was approved by the Human Research Ethics Committee at the QIMR Berghofer Medical Research Institute. Subjects were assessed at ages 12, 14, and 16 for psychiatric symptoms and blood was drawn at these ages. At age 16, twins completed an extensive cognitive test battery, including an IQ assessment. For TL measurement, mean age at accession of the DNA used was 14 years (*SD* 2.5 years) and only accessions collected on the same day for co-twins were used, which was the case for > 72.2% of twin pairs.

We used data only for pairs with TL measures available for both twins, and the present analyses include three overlapping subsamples of 1,772 subjects: (1) TL and birth weight were available for 242 MZ and 245 same sex DZ complete twin pairs; (2) TL and IQ for 203 MZ and 209 same sex DZ twin pairs; and (3) TL and mental well-being for 137 MZ and 171 DZ same sex twin pairs.

Measures: Psychiatric symptoms were assessed with the Somatic and Psychological Health Report (SPHERE), a 34-item self-report questionnaire that has been developed to screen for mental disorders such as anxiety and depression in general practice (Hickie et al., 2001a; Hickie, et al., 2001b). Participants indicated if they had been troubled by symptoms over the past few weeks, making one of three response choices: *sometimes/never* (coded as zero); *often; most of the time* (each coded as 1). The total score of all 34 items was used as a measure of anxiety/depression.

At age 16, twins completed three verbal subtests (Information, Arithmetic, Vocabulary) and two performance subtests (Spatial and Object Assembly) from a shortened version of the Multidimensional Aptitude Battery (Jackson, 1984), an extensive cognitive test battery that measures, among others, the IQ.

Mothers of twins and siblings were asked for the birth weight of their children at both the age 12 and 14 visits, or at the age 16 visit, for those twins who were not assessed at age 12 or 14. The birth weight reported at age 12 was used for analyses, being the more proximal measure. If reported birth weight at age 12 was not available, reported birth

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weight at age 14 or 16 was used. The correlation between the reports at age 12 and 14 respectively, was 0.95.

Replication sample: Netherlands Twin Register (NTR)

Subjects: The NTR was established in the late 1980s (Boomsma et al., 2002; 2006). Most twins were recruited through city councils between 1990 and 1993, when they were adolescents or young adults. Detailed information on the longitudinal survey study and the NTR biobank project has been provided previously (Boomsma et al., 2006; Willemsen et al., 2013). The current analysis included twins who participated in the NTR biobank project, conducted between 2004 and 2008 (Willemsen et al., 2010). Data on birth weight and TL were available for 514 complete MZ pairs and for 233 DZSS pairs, of whom 437 MZ pairs and 176 DZSS pairs also had data on depression. Blood was drawn when the twins were aged 17–80 (mean age at TL measurement 36 years, *SD* 11 years). Informed consent was obtained from participants and study protocols were approved by the Medical Ethics Committee of the VU University Medical Centre.

Measures: Data on birth weight were collected as part of multiple NTR surveys and projects. Data reported by the twins themselves and/or by their parents were combined and consistency across family members and time was checked. When multiple data points differed, the average was taken, but only if the difference was less than 200 grams. When possible, data were also checked against reports from National Youth Health Services.

Data on depression were collected in multiple NTR surveys. For the current analyses, depression scores from NTR surveys 5 (conducted in 2000), 6 (2002), 8 (2009), and 9 (2011) were used. In NTR surveys 5 and 6, the Young Adult Self-Report Score (YASR; Achenbach, 1997) was used to score depressive symptoms and in survey 8 and 9, the Adult Self-Report (Achenbach & Rescorla, 2003) was collected as part of the survey. Within surveys, depression scores were converted to *z* scores. To obtain one score for each subject, the depression *z* score was selected from the time point closest to the moment of blood draw, for which both twins had data (i.e., data for co-twins were selected from the same survey).

Replication sample: Melbourne peri/postnatal epigenetics twin study (PETS)

The longitudinal Peri/postnatal Epigenetics Twin Study (PETS) is a cohort of 251 twin pairs and their mothers, recruited midway through pregnancy (Loke et al., 2013; Saffery et al., 2012). To date, lifestyle/environment data and tissue samples have been collected at birth and at 18 months of age, with six-year follow-up currently underway. Mothers are predominantly of white European descent. For the current study, we used purified cord blood mononuclear cells (CBMCs) from MZ twin pairs that were either highly discordant (7 pairs, birth weight difference 456 g to 991 g, mean difference 613 g) or concordant in birth weight (12 pairs, birth weight difference 40 g to 155 g, mean difference 91 g).

TL measurement and quality control analysis

TL was measured in the Brisbane and Amsterdam samples in the same laboratory at the University of Leicester, and the Melbourne samples in the laboratory at the Murdoch Childrens Research Institute. Both laboratories used the same established quantitative PCR–based technique (Cawthon, 2002, 2009). In brief, this method expresses TL as a ratio (T/S) of telomere repeat length (T) to copy number of a single copy gene (S), in each sample. Samples were measured in duplicate for both the telomere (T) and *36B4* (S) assays. The single-copy gene, *36B4*, serves as a reference gene in the conventional qPCR for telomere measurement (Cawthon, 2002). To minimize inter-assay variation, the T/S ratio was calculated relative to a calibrator sample (DNA from the K562 cell line) run on each PCR plate. Any sample that was outside the linear range of the assay was diluted and re-run until results were observed within the linear range. For quality control, all samples were checked for concordance between duplicate values. Samples showing a difference between the duplicate measurements of greater than 0.2 cycles were excluded and rerun. To ensure reproducibility of the assay, samples were regularly rerun at random on a different day and/or machine. All samples reproduced well ($r^2 = 0.97$, $p < .0001$).

Statistical analyses

In the Brisbane and Amsterdam twins, T/S ratio was *z*-standardized and birth weight was transformed using the square root (Blair et al., 2005). In the Brisbane twins, Blom rank normalization was applied for the IQ score, and the SPHERE-34 item responses of the repeated measurements at ages 12, 14 and 16 were transformed into theta scores according to the principles of Item Response Theory (Wray et al., 2008). In the Amsterdam twins, the depression score was *z*-standardized. Analyses were calculated in IBM SPSS statistics 20.0 (http://www.spss.com). TL was corrected for sex, age at blood withdrawal, and age squared. To minimize the impact of age and laboratory batch variation, we used an intra-twin pair design, using only DZSS pairs. Where intra-pair differences were being correlated for different variables, the same order of twins was preserved for each phenotype.

Results

Table 1a shows the number of pairs and intra-pair differences for the raw TL, birth weight, IQ, and anxiety/depression scores in the three overlapping subsamples from Brisbane, and Table 1b likewise for the Amsterdam and Melbourne samples. Mean age of samples at TL analysis for Brisbane was 14 (*SD* 2.5), Amsterdam 36 (*SD* 11), and Melbourne twins were all newborns.

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TABLE 1a

Absolute Intra-Pair Differences (Diff.) for Monozygotic and Dizygotic Twin Pairs of Raw Telomere Length (TL), Birth Weight, IQ, and Anxiety/Depression Scores in the Three Subsamples of the Brisbane (Discovery) Sample

	TL and birth weight	TL and IQ	TL and anxiety/depression
MZ			
Number of pairs	242	203	137
Sex	129 female, 113 male	112 female, 91 male	78 female, 59 male
Absolute intra-pair diff.			
TL (mean/*SD*)	0.29 (0.28)	0.28 (0.27)	0.30 (0.30)
Birth weight in g (mean/*SD*)	287 (260)		
IQ (mean/*SD*)		5.91 (4.67)	
anxiety/depression (mean/SD)			0.54 (0.46)
DZ same sex			
Number of pairs	245	209	171
Sex	124 female, 121 male	108 female, 101 male	94 female, 77 male
Absolute intra-pair diff.			
TL (mean/*SD*)	0.42 (0.33)	0.41 (0.33)	0.40 (0.33)
Birth weight in g (mean/*SD*)	273 (258)		
IQ (mean/ *SD*)		9.88 (7.37)	
Anxiety/depression (mean/SD)			0.71 (0.54)

Note: Differences = diff., TL = telomere length, Monozygotic = MZ, Dizygotic = DZ.

TABLE 1b

Absolute Intra-Pair Differences for MZ Twin Pairs of Raw TL, Birth Weight, and Depression Scores in the Two Replication Samples

	Amsterdam		Melbourne
	TL and birth weight	TL and depression	TL and birth weight
MZ			
Number of pairs	514	437	19
Sex	377 female, 137 male	328 female, 109 male	10 female, 9 male
Absolute intra twin pair diff.			
TL (mean/SD)	0.29 (0.27)	0.30 (0.26)	0.30 (0.27)
Birth weight in g (mean/SD)	282 (298)		283 (284)
Depression (mean/SD)		0.76 (0.72)	
DZ same sex			
Number of pairs	233	176	
Sex	168 female, 65 male	135 female, 41 male	
Absolute intra twin pair diff.			
TL (mean/SD)	0.40 (0.35)	0.39 (0.35)	
Birth weight in g (mean/SD)	315 (298)		
Depression (mean/SD)		0.94 (0.93)	

TABLE 2a

Pearson Correlations of Intra-Pair Differences in Telomere Length (TL), Birth Weight, IQ, and Anxiety/Depression in Monozygotic (MZ, Above the Diagonal) and Same Sex Dizygotic (DZ) Twin Pairs (Below Diagonal) of the *Brisbane* Sample. *p* Values are Two-Tailed. M Z twins (113– 242 pairs)

Intra-pair differences	TL	Birth weight	IQ	SPHERE
TL	1	0.149*	0.285***	0.079
Birth weight	0.048	1	0.269***	-0.039
IQ	0.149*	0.204**	1	-0.103
Anxiety/depression (SPHERE)	0.054	0.0004	-0.09	1

Note: D Z twins (171–245 pairs)
* $p \leq 0.05$ ** $p \leq 0.01$ *** $p \leq 0.001$.

Pearson correlations between intra-pair differences in TL, birth weight, IQ, and anxiety/depression in MZ and DZ twin pairs are shown in Table 2. We found a significant correlation between intra-pair differences in TL and birth weight in MZ twin pairs ($r = 0.149$, $p = .021$, 95% CI: 0.023–0.270) with the heavier twin having higher TL, but not in DZ pairs ($r = 0.048$, $p = 0.457$, 95% CI: –0.078–0.172). We also found a significant correlation between intra-pair differences in TL and IQ in MZ ($r = 0.285$, $p < 0.001$, 95% CI: 0.153–0.407), and in the DZ pairs ($r = 0.149$, $p = 0.031$, 95% CI: 0.014–0.279). Correlations between intra-pair differences in birth weight and IQ are positive and appreciable in both MZ ($p = 0.269$, $p < 0.001$, 95% CI: 0.138–0.391) and DZ twins ($r = 0.204$, $p = 0.003$, 95% CI: 0.070–0.331), indicating that the heavier twin at birth has higher IQ, and these correlations remained significant when controlled for

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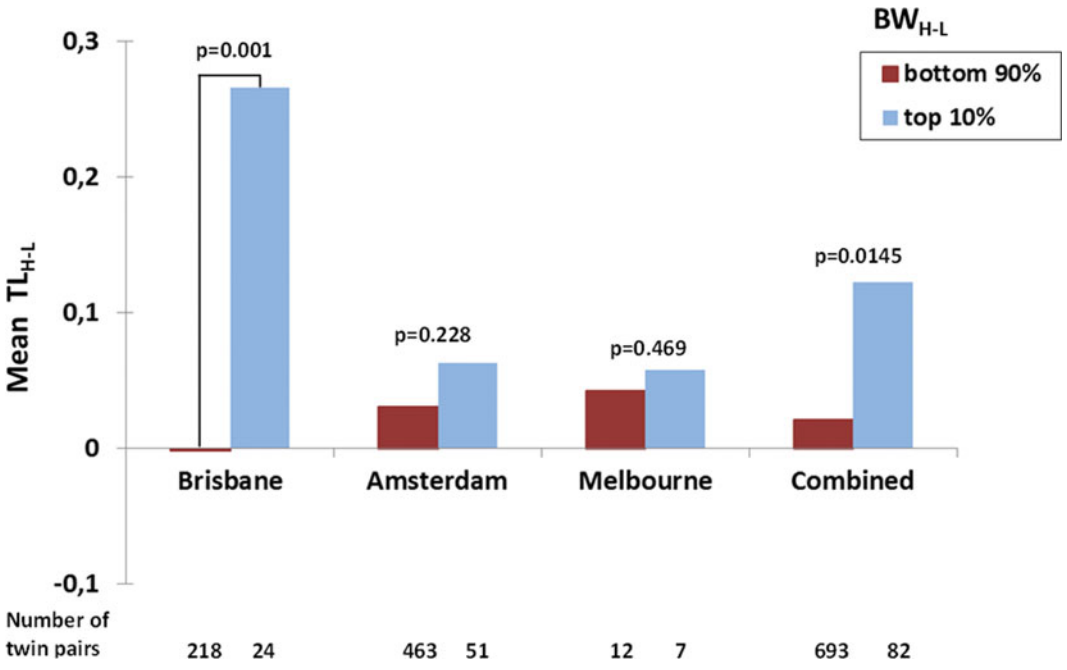

FIGURE 1

(Colour online) Mean TL_{H-L} (Difference in TL between the Heavier and the Lighter Twin) in the Top 10% and Bottom 90% of BW^{H-L} Values (Difference in BW between the Heavier and the Lighter Twin) in the Brisbane, Amsterdam, and Melbourne and Combined Monozygotic Twin Pairs.

TABLE 2b

Pearson Correlations of Intra-Pair Differences in TL, Birth Weight, and Depression in MZ (Above the Diagonal) and Same Sex DZ Twin Pairs (Below Diagonal) of the *Amsterdam* Sample. *p* Values are Two-tailed MZ twins (437–514 pairs)

Intra-pair differences	TL	Birth weight	Anxiety/depression
TL	1	0.092*	-0.056
Birth weight	-0.037	1	-0.043
Anxiety/depression	-0.108	0.027	1

Note: D Z twins (176–233 pairs)
* $p \leq 0.05$ ** $p \leq 0.01$ *** $p \leq 0.001$

birth weight. Correlations with anxiety/depression are all small and non-significant, indicating that low birth weight, shorter TL or lower IQ are not associated with teenage mental health.

In the replication sample from Amsterdam, there was a significant correlation between the intra-pair difference in TL and birth weight in the MZ ($r = 0.092$, $p = 0.038$, 95% CI: 0.006–0.177), but not in the DZ twin pairs ($r = -0.037$, $p = 0.572$, 95% CI: –0.165–0.092). We found no evidence for a relationship between intra-pair difference in depression and intra-pair difference in TL, either in MZ twins ($r = -0.056$, $p = 0.244$, 95% CI: –0.149–0.038) or DZ twins ($r = -0.108$, $p = 0.155$, 95% CI: –0.252–0.041). Neither did the intra-pair difference in depression correlate with the intra-pair difference in birth weight in MZ ($r = -0.043$, $p = 0.365$, 95% CI: –0.136–0.051) or DZ twin pairs ($r = 0.027$, $p = 0.720$, 95% CI: –0.121–0.174). These findings support the results in the Brisbane sample.

To further explore whether the correlation of the intra-twin pair difference in birth weight and TL was carried by MZ twin pairs with an extreme difference in birth weight, we calculated the difference in birth weight between the heavier and the lighter twin (BW_{H-L}) and the corresponding difference TL_{H-L}. We then split the Brisbane MZ twin pairs into two groups, that is, in the most birth weight discordant twin pairs (top 10%: $N = 24$ twin pairs with difference in birth weight ranging between 652 and 1,200 g and a mean difference of 882 g) and least birth weight discordant in twin pairs (bottom 90%: $N = 218$ twin pairs with difference in birth weight ranging between 0 g and 624 g with a mean difference of 222 g). The Amsterdam MZ twin pairs were also split into the top 10% (51 pairs, birth weight difference 684–1,500 g, mean difference 971 g) and bottom 90% birth weight difference groups (463 pairs, birth weight difference 0–650 g, mean difference 206 g). For the Melbourne sample, we compared the mean of the seven most birth weight discordant pairs compared with the 12 least discordant (Figure 1). For all three samples, the results went in the same direction of the most birth weight discordant twin pairs having larger TL differences, with the lighter twin having shorter TL, but *t*-tests revealed that this difference was only significant for Brisbane ($p = 0.001$, one-tail), but not for Amsterdam ($p = 0.288$) or Melbourne ($p = 0.469$). The combined one-tail *p* value for all three samples is $p = 0.0145$.

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TABLE 3

Significance of Association in Monozygotic (MZ) Pairs of the Concordance of Direction of the $Twin_1$–$Twin_2$ Differences in Telomere Length with the $Twin_1$– $Twin_2$ Differences in Birth Weight, Depending on Cut-Off for Absolute Birth Weight Difference (BW_{H-L}), by Study and for the Combined Sample. One-Tailed *p*-Values are Given

	Cut-off BW_{H-L}													
	> 0 g		> 100 g		> 200 g		> 300 g		> 400 g		> 500 g		> 600 g	
	n	*p*	*n*	*p*	*n*	*p*	*n*	*p*	*n*	*p*	*n*	*p*	*n*	*p*
Brisbane	229	0.318	174	0.219	116	0.500	79	0.316	60	0.401	42	0.114	27	0.244
Amsterdam	459	0.064	296	***0.013***	234	***0.017***	184	***0.027***	145	0.081	81	0.135	57	0.377
Melbourne	19	0.395	11	0.348	7	0.476	7	0.476	7	0.476	4	0.75	3	
Combined sample	707	***0.042***	481	***0.006***	357	***0.026***	270	***0.020***	212	0.057	127	***0.026***	87	0.198
$Phi_{combined\ sample}$	0.068		0.118		0.108		0.133		0.118		0.190		0.117	
$OR_{combined\ sample}$	1.314		1.616		1.552		1.738		1.625		2.240		1.657	

Our top 10% cut-off was somewhat arbitrary and, being a relative measure, differs between samples, so we further investigated in an explorative way the influence of the absolute threshold in birth weight difference (BW_{H-L}) in grams on the association between birth weight and TL difference. For this purpose, we dichotomized both birth weight difference and TL difference as follows: birth weight difference was coded as '+' if twin 1 was the heavier twin and '–' if twin 2 was the heavier twin. Similarly, TL difference was coded as + if twin 1 had longer telomeres and – if twin 2 had longer telomeres. A chi-square contingency test was then applied to test whether the heavier twin also showed larger TL and vice versa. We did this at different BW_{H-L} cut-offs (> 0 g, > 100 g, > 200 g, > 300 g, > 400 g, > 500 g, > 600 g) in the Brisbane, Amsterdam and Melbourne MZ twin pairs and the combined MZ twin pair sample; that is, first we included all pairs with a $BW_{H-L} > 0$ g, then all pairs with a $BW_{H-L} > 100$ g and so on. If there is a very strong relationship between birth weight discordance and TL difference, then we should expect to see a stronger association in twin pairs with a higher minimum birth weight difference. In fact, we observed an increase of the effect size (Phi, OR) until a cut-off at BW_{H-L} 500 g, and then the effect size decreased, probably because of limited power due to decreasing number of twin pairs per cell (Table 3).

Discussion

We assessed the association of TL with birth weight, IQ and anxiety/depression in a large Brisbane sample of MZ and same sex DZ twin pairs, making use of intra-pair differences. In MZ twin pairs, the intra-pair difference in TL was significantly correlated with the intra-pair difference in birth weight ($r = 0.149$, $p = 0.021$), but not in DZ twin pairs ($r = 0.048$). We replicated this pattern in the twin pairs from Amsterdam (MZ: $r = 0.092$, DZ: $r = –0.037$), suggesting that the association between birth weight and TL is not mediated by genetic factors but by non-shared environmental factors. In the Brisbane MZ twin pairs, the intra-pair difference in TL was correlated with the intra-pair difference in IQ (0.285, $p < 0.001$); also, the intra-pair difference in IQ was correlated with the intra-pair difference in birth weight (0.269, $p < 0.001$). Both correlations were lower but substantial in the DZ twin pairs ($r = 0.149$, $p = 0.031$; $r = 0.204$, $p = 0.003$, respectively) suggesting that these associations are mediated by environmental and/or non-shared genetic factors.

We further hypothesized that if the same factors that cause an extreme discordant birth weight difference in the MZ twin pairs also influence TL length in both co-twins, then the correlation between TL and birth weight should be stronger in the MZ twin pairs most highly discordant in birth weight. Indeed, in the Brisbane MZ twin pairs the correlation between TL and birth weight was only significant in 10% of the most birth weight discordant MZ twin pairs but not in the twin pairs with a low-to-medium birth weight difference. An effect in the same direction – – although non-significant — was also present in the MZ twin pairs from Amsterdam and a second replication sample from Melbourne. In all three samples, the most birth weight discordant twin pairs had larger TL differences, with the lighter twin having shorter TL. Further analysis using increasing thresholds of MZ birth weight discordance showed steadily increasing effects on TL up to a 500 g discordance, beyond which our number of twin pairs per cell became too small to obtain reliable results.

These findings indicate that prenatal factors that decrease birth weight in one twin more than the other have a negative influence on TL in the lighter twin. This relationship between low birth weight and shorter TL has been found previously in placenta samples (Davy et al., 2009) but was not found in a small study measuring TL in cord blood (Akkad et al., 2006) nor in three cohorts (including 124 MZ and DZ twin pairs) from Finland (Kajantie et al., 2012). These negative reports do not necessarily contradict our findings. In our study, we only observed an association between birth weight and TL within MZ twin pairs, most strongly in those highly discordant for birth weight. We did not observe an association when analyzing the twins in a

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conventional between-subject analysis, even allowing for relatedness, and when analyzing within twin pair differences in DZ pairs. Thus one could hypothesize that in DZ twins and the general population, the genetic effects influencing TL may override the perinatal factors. Also, we found the strongest associations between the intra-pair difference in TL and birth weight in the Brisbane sample, in which TL was measured at a mean age of 14 years, and a smaller association in the Amsterdam sample where TL was measured at a mean age of 36 years. The Finnish twins were young adults when TL was assessed. In older age, the effects of prenatal stress on TL may weaken and be overlaid by other postnatal factors influencing TL such as, for example, environmental stress factors (Ahola et al., 2012; Drury et al., 2012; 2014; Humphreys et al., 2012; Kananen et al., 2010; O'Donovan et al., 2011; Shalev et al., 2013b; Surtees et al., 2011; Tyrka et al., 2010; Uchino et al., 2012).

Our findings suggest that low birth weight per se is not associated with shorter TL, but that specific non-shared prenatal factors in MZ twins lead to TL shortening. Prenatal factors that could potentially account for our findings are placental differences between MZ and DZ twins and between monochorionic and dichorionic MZ twins (for review, see Loos et al., 2009). Peripheral umbilical cord insertion on the placenta and fused dichorionic placentas occur more often or have less favorable outcomes (including lower birth weight) in MZ than in DZ twins. Also, monochorionic MZ twins who share one placenta have a higher prevalence of vascular anastomoses, velamentous cord insertion and single umbilical arteries, which may result in an unequal supply of blood to one of the co-twins. These placental differences between MZ co-twins and MZ and DZ twins may account for our finding that the intra-twin pair correlation between TL and birth weight was only significant in the highly birth weight discordant MZ twin pairs, and not in the DZ pairs. A very severe form of unfavorable placentation of one twin is the twin-to-twin transfusion syndrome (TTTS). TTTS complicates 8–10% of twin pregnancies with monochorionic diamniotic (MCMZ) pregnancy (Simpson, 2013). In such cases, connections (anastomoses) are formed between placental blood vessels from each twin. This results in unequal blood flow between the twins, which in turn causes one sac to increase in size at the expense of the other, resulting in high birth weight discordance (Simpson, 2013). As a result, both twins have a higher risk of mortality and morbidity including compromised neurodevelopment. We hypothesized that a common cause of the correlation of short TL with lower IQ was the extremely low birth weight of twins who had suffered TTTS. However, direct reporting of TTTS was only available for the Melbourne sample, and the one confirmed MZ pair with TTTS had the second highest birth weight difference (746 g) and the fifth highest difference in TL.

We also observed a higher correlation of the intra-pair differences in TL and IQ and IQ and birth weight in MZ pairs, suggesting that the same non-shared prenatal factors that account for the association of TL and birth weight may also mediate the association between TL and IQ, that is, less favorable placentation in MZ twins may increase the risk for placental undersupply in one co-twin and affect cognitive ability in later life.

Nutrition is an important factor in the development of the brain (Kretchmer et al., 1996). Micronutrient deficiencies (iodine, iron, zinc, and vitamin B-12) during pregnancy and malnutrition from early childhood on (Engle & Fernandez, 2010; Grantham-McGregor, 1995) have found to negatively influence neurocognitive development and cognitive function (Black, 2003; Blusztajn & Mellott, 2012; Larque et al., 2012; Mitka, 2013; Nyaradi et al., 2013; Zimmermann, 2007). Also, associations between low birth weight and cognition have been described repeatedly (Shenkin et al., 2004; Singh et al., 2013). Finally, there are findings that suggest an influence of micronutrient deficiencies on TL (Moores et al., 2011; Paul, 2011). All these studies in combination with our findings suggest that placental undersupply may have a negative influence on TL and IQ in adolescence and young adulthood. The correlations between TL and IQ (0.149, $p = 0.031$) and IQ and birth weight ($r = 0.204$, $p = 0.003$) in DZ twins however suggests that in these associations non-shared genetic or further non-shared environmental effects that also affect DZ twins may also play a role.

We did not observe an association between TL and anxiety/depression, either in the Brisbane sample or in the replication sample from Amsterdam. Previous studies on the association between TL and longitudinally assessed psychiatric symptoms and psychiatric disorders are largely inconsistent. Hoen et al. (2013), for example, reported in a prospective study that persistence of anxiety disorders was associated with shorter TL measured after 2 years follow-up, but depressive disorders did not. Their results indicate that at least anxiety symptoms may have a negative impact on TL. The authors argue that the physiological hyperarousal and physiological stress associated with anxiety disorders may cause telomere damage, consistent with other studies linking psychological stress with shorter TL (Ahola et al., 2012; Drury et al., 2012; 2014; Entringer et al., 2011; 2013; Epel et al., 2004; Humphreys et al., 2012; Kananen et al., 2010; O'Donovan et al., 2011; Price et al., 2013; Shalev et al., 2013a; Shalev et al., 2013b; Surtees et al., 2011; Tyrka et al., 2010; Uchino et al., 2012). On the other hand, there are also studies that do not support such an association, among them a most recent study assessing life stress in a 30-year birth cohort (Jodczyk et al., 2014; Phillips et al., 2013; Rius-Ottenheim et al., 2012). Our findings thus add further support to the assumption that shorter TL is not per se a risk factor for psychiatric disorders. Rather, psychiatric disorders and the psychological and physiological stress associated with them may possibly influence TL shortening.

Our study has several strengths. First, to our knowledge, it is the largest study and the largest twin study to

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date investigating the relation between TL and IQ, and the largest twin study investigating the association between TL and birth weight and TL and anxiety/depression. Second, our study design, that is, the investigation of correlations of intra-pair differences separately in MZ and DZ pairs, allowed us to disentangle whether non-shared genetic factors and/or environmental factors account for the association between TL and cognition. Finally, we replicated our results that TL does not appear to affect anxiety/depression later in life, in two independent twin samples.

Our study also has several limitations. First, we did not consider — because data were not available — monochorionic and dichorionic twins separately in our analyses, which may have elucidated whether our findings are the result of these placental factors. Second, we were not able to disentangle potential shared environmental effects such as, for example, maternal psychosocial stress during pregnancy, on the association of TL and birth weight. Third, in the Brisbane sample, anxiety/depression was measured in adolescence and we do not know whether our study participants will develop psychological problems at some point later in life (they are currently being followed up in their 20s). However, in the Amsterdam sample depression was measured in middle age and still we saw no association between TL and depression. Fourth, TL was not measured at birth in the Brisbane and Amsterdam twins. However, it was measured at birth in the Melbourne sample in which we observed a correlation between TL and birth weight in the same direction as in the two other samples — although non-significant. Fifth, although the SPHERE is a screening instrument for mental disorders such as anxiety and depression in general practice (Hickie et al., 2001a; Hickie et al., 2001b), it is a self-rating questionnaire and not a diagnostic instrument such as, for example, the SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders), which gives valid psychiatric diagnoses. Sixth, stochastic effects have also influenced our intra-twin pair correlations; however, the magnitude of these effects is unknown. Finally, one of our most important results — the correlation between TL and birth weight in the 10% most birth weight discordant MZ twin pairs — was non-significant in the Amsterdam and Melbourne samples. In the Melbourne sample, the directional effect is there throughout the range of birth weight discordance (Table 3), but the small sample size, which decreases the power to detect an effect, may explain the non-significance. In the Amsterdam sample, the higher age of the twins may be an important factor in diminishing the effect of birth weight on current TL. Nevertheless, as Table 3 shows, in the Amsterdam sample the directional effect is there throughout the range of MZ birth weight discordance and is significant at the 100 g, 200 g, and 300 g thresholds, even with a low-powered nonparametric test.

In summary, our findings suggest that environmental effects that occur prenatally and decrease birth weight have a negative influence on TL. Our findings further indicate that the association between TL and IQ may partly be driven by the same perinatal effects that decrease birth weight, although the positive correlation in DZ twins suggests genetic factors may also play a part. Finally, we have shown that twin pairs who are discordant for TL and birth weight do not differ in anxiety/depression later in life.

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