ORIGINAL RESEARCH

Marital status, telomere length and cardiovascular disease risk in a Swedish prospective cohort

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2019-315629).

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Received 1 July 2019
Revised 18 October 2019
Accepted 25 October 2019
Published Online First
14 November 2019

Linked

► http://dx.doi.org/10.1136/heartjnl-2019-316042

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To cite: Chen R, Zhan Y, Pedersen N, *et al*. *Heart* 2020;**106**:267–272.

ABSTRACT

Objective To investigate if marital status is associated with risk of cardiovascular disease (CVD) and to explore the potential influence of leucocyte telomere length (LTL), a marker of biological ageing, on such association.

Design Population-based prospective cohort study

Settings Swedish Twin Registry.

Participants Based on the Screening Across the Lifespan Twin Study from the Swedish Twin Registry, we included 10 058 twins born between 1900 and 1958 who underwent an interview between 1998 and 2002 during which information about marital status was collected. Blood samples from these participants were subsequently collected between 2004 and 2008 and used for LTL assessment using quantitative PCR technique.

Main outcome measures Incident cases of CVD were identified through the Swedish Patient Register and Causes of Death Register through December 31, 2016. Multivariable linear regression and Cox proportional hazards regression models were used to estimate the regression coefficients (βs) and HRs with 95% CIs respectively. Potential confounders included age, sex, educational attainment and body mass index.

Results A total of 2010 participants were diagnosed with CVD during a median follow-up of 9.8 years. LTL was shorter among individuals living singly, including those who were divorced or separated (β:−0.014, 95% CI: −0.035, 0.007), widowed (β:−0.035, 95% CI: −0.061, −0.010), or living alone (β:−0.033, 95% CI: −0.052, −0.014), than individuals who were married or cohabitating. One SD increase of LTL was associated with a lower risk of CVD (HR: 0.79, 95% CI: 0.66, 0.93). Individuals who were divorced or separated, widowed, or living alone had a higher risk of CVD than individuals who were married or cohabitating. The summary HR of CVD was 1.21 (95% CI: 1.08, 1.35) when comparing individuals who were living singly, regardless of reason, with the individuals who were married or cohabitating. LTL appeared to mediate little of the association between marital status and CVD (HR additionally adjusted for LTL: 1.20; 95% CI: 1.08, 1.34).

Conclusions Living singly, regardless of reason, was associated with a shorter LTL and a higher risk of CVD. The association between marital status and CVD was however not greatly attributable to telomere shortening.

INTRODUCTION

Marital status has been reported to have influence on the risk of cardiovascular disease (CVD) since long.[1] A recent meta-analysis summarised findings of existing prospective cohort studies and showed that individuals who were single, divorced, or widowed had a higher risk of CVD than individuals who were married.[2] Similar results have been reported for CVD-specific mortality.[3] Different mechanisms may underlie the link between marital status and CVD. Cohabitation is associated with health consciousness and healthcare use,[4] and as a result, influences the opportunities of early intervention for CVD risk factors[5] and adherence for such intervention.[6] This link may also be attributable to psychological distress in relation to altered marital status. For instance, loss of a spouse due to death yields a higher risk of depressed mood, poor social functioning,[7] reduced quality of life,[8] and an increased risk of coronary heart disease.[9] Psychological distress has further been linked with hypertension, dyslipidemia, glycaemic dysregulation and atherosclerosis,[10] all established risk factors for CVD.

Telomeres are sequences of nucleotides at the end of chromosomes that become shorter with every cell division. Each time a cell divides, telomeres become shorter. Telomere shortening is associated with ageing, mortality and aging-related diseases.[11] The relationship between telomeres and CVD is well studied with mostly consistent results across different study populations. Shortened telomeres are associated with increased risks of coronary heart disease, stroke, myocardial infarction and type 2 diabetes mellitus.[12 13] Mendelian Randomisation studies have further suggested causal relationships between telomere length (TL) and these outcomes.[14] Telomere shortening has also been associated with psychological distress. A recent meta-analysis found that self-reported perceived psychological distress was associated with a small but statistically significant decrease in TL, and concluded that the association may be stronger for major and chronic stressors.[15] Marital status has been associated with TL in three studies, which showed consistently that non-cohabitation was associated with a reduced TL.[16–18] The potential role of TL in the association between marital status and CVD has, however, never been assessed.

In this study, we aimed to investigate the association between marital status and risk of CVD, and to examine whether leucocyte TL (LTL), a marker of biological ageing and psychological distress, contributes to such an association, using a population-based cohort from the Swedish Twin Registry.[19–21]

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Table 1 Characteristics of study participants

	Men	Women	Total
N	4833	5225	10 058
Age (years, mean±SD)	59.3±7.8	58.3±7.8	58.8±7.8
Body mass index (kg/m^2, mean±SD)	25.5±2.9	24.5±3.6	25.0±3.3
Educational attainment (N (%))			
0–9 years	1486 (30.7)	1505 (28.8)	2991 (29.7)
>9–12 years	2085 (43.1)	2230 (42.7)	4315 (42.9)
>12 years	1262 (26.1)	1490 (28.5)	2752 (27.4)
Marital status (N (%))			
Married or cohabiting	4088 (84.6)	3936 (75.3)	8024 (79.8)
Divorced or separated	257 (5.3)	439 (8.4)	696 (6.9)
Widowed	108 (2.2)	382 (7.3)	490 (4.9)
Living alone	380 (7.9)	468 (9.0)	848 (8.4)
Smoking (N (%))			
Never	717 (14.8)	1483 (28.4)	2200 (21.9)
Only tried	926 (19.2)	931 (17.8)	1857 (18.5)
Sometimes	371 (7.7)	643 (12.3)	1014 (10.1)
Regularly	2818 (58.3)	2168 (41.5)	4986 (49.6)
Physical activity (N (%))			
Never	1103 (23.8)	1034 (20.6)	2137 (22.2)
Sometimes	1251 (27.0)	1221 (24.4)	2472 (25.6)
Regularly	2274 (49.1)	2756 (55.0)	5030 (52.2)
Hypertension (N (%))	1037 (21.5)	1198 (22.9)	2235 (22.2)
Diabetes (N (%))	235 (4.9)	136 (2.6)	371 (3.7)
Dyslipidemia (N (%))	742 (15.4)	575 (11.0)	1317 (13.1)

METHODS

Study population

The Screening Across the Lifespan Twin (SALT) study was initiated in 1998 to screen for common complex diseases among twins included in the Swedish Twin Registry.[19 20] A total of 61 767 twins born between 1900 and 1958 were invited to participate in the study. Data collection was performed with a computer assisted telephone interview by trained staff with adequate medical background. A number of questions including marital status, educational attainment and lifestyle factors were asked. Data collection was completed in December 2002 with 44 919 participants recruited. A subsample of these participants (n=22 390) was later invited to donate blood samples in the TwinGene project between 2004 and 2008.[21] These participants were asked to make appointments at their local healthcare facilities in the morning, to ensure that the blood samples would reach the Karolinska Institutet Biobank the following day by overnight transportation. In total, 12 046 participants donated blood samples.

Marital status

Marital status was assessed by a question '*What is your present marital status?*' with the following options: *married, cohabiting, divorced, separated, widowed, or living alone (ie, living without a partner and not divorced, separated, or widowed)*.

TL assessment

LTL was measured from leucocytes in whole blood. Standard quantitative PCR (qPCR) technique was applied to measure LTL as described previously.[22] In brief, telomere (T) and single copy gene (S) quantity were measured and a T/S-ratio was calculated. One or several reference samples were included in all runs and a relative LTL was calculated for each sample. Batch effect was corrected for each measurement plate, through linear regression models where LTL T/S-ratio was used as the dependent variable and the different plate identification numbers were used as independent variables. Thus, the T/S-ratio measurements were adjusted for plate number by calculating residuals from the linear regression, and residuals were then scaled back to T/S--ratio by adding the global mean to each value.

Cardiovascular disease ascertainment

CVD diagnosis was defined as either a hospitalisation or an outpatient visit for which CVD was identified as the main discharge diagnosis (according to the Swedish Patient Register) or a death with CVD as the underlying cause of death (according to the Causes of Death Register). The Swedish Patient Register includes hospital discharge records since 1964/1965 (national coverage since 1987) and hospital-based outpatient specialist visits since 2001. The Swedish Causes of Death Register includes nationwide information on date of death and causes of death since 1961. Diagnoses were coded according to the Swedish revisions of the International Classification of Disease (ICD) eighth to 10th versions codes. The following codes for ischaemic heart disease, myocardial infarction (MI), angina, atherosclerosis and peripheral arterial diseases were included in the study: 410, 411, 412, 413, 414, 440 and 443.90 in ICD-8 (before 1987); 410, 411, 412, 413, 414, 440, and 443X in ICD-9 (1987–1996); and I20, I21, I22, I23, I24, I25, I70 and I73.9 in ICD-10 (1997 onward). All individuals were followed from date of blood sample collection until the date of CVD diagnosis, date of death, or December 31, 2016, whichever came first.

Covariates

In the main analysis, we considered variables that have been associated with both marital status and risk of CVD as potential confounders for the associations under study, including educational attainment[23 24] and body mass index (BMI),[25 26] in addition to age and sex. Educational attainment was defined as the highest educational level obtained and was classified as 0–9 years, >9–12 years and >12 years. BMI was calculated from self-reported body weight and height. Of the original 12 046 participants, 1319 individuals did not have LTL measured and 669 individuals had prevalent CVD or LTL values out of the range of four SD. We included in the final analysis 10 058 participants, who were free of CVD at the time of blood sample collection, and with measurements of LTL and information on age, sex, marital status, educational attainment and BMI.

In a secondary analysis, several other risk factors for CVD, including lifestyle factors (ie, physical activity and smoking) and metabolic disorders (ie, diabetes, hypertension and dyslipidemia) were also considered.[26–29] Because these factors have been suggested as potential health consequences of marital status,[30–33] we considered them as potential mediators linking together marital status and CVD. Physical activity was categorised as 'never', 'sometimes' and 'regularly', based on a question regarding annual exercise pattern. Smoking status was classified as 'never', 'only tried', 'sometimes' and 'regularly'. Likewise, information on hypertension, diabetes and dyslipidemia was collected from questions concerning physician-diagnosed disorders during the interview.

Statistical analysis

Multivariable linear regression models were used in the main analysis to estimate the association (β and 95% CI) between

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Table 2 Association between marital status and telomere length

	Men (β (95% CI))	Women (β (95% CI))	Total (β (95% CI))
Marital status			
Married or cohabiting	Ref	Ref	Ref
Divorced or separated	−0.023 (−0.055, 0.009)	−0.010 (−0.037 to 0.018)	−0.014 (−0.035 to 0.007)
Widowed	−0.034 (−0.084, 0.015)	−0.040 (−0.070 to −0.009)	−0.035 (−0.061 to −0.010)
Living alone	−0.007 (−0.034, 0.020)	−0.056 (−0.082 to −0.029)	−0.033 (−0.052 to −0.014)
Married or cohabiting	Ref	Ref	Ref
Living singly*	−0.017 (−0.037 to 0.003)	−0.035 (−0.053 to −0.017)	−0.027 (−0.040 to −0.014)

Models adjusted for age, sex, educational attainment and body mass index.
*Living singly includes divorced or separated, widowed and living alone.

marital status and LTL, after adjusting for age, sex, educational attainment and BMI. We then fitted Cox proportional hazards models to assess the association of LTL (both per one SD increase and categorised according to tertiles) with the risk of CVD as well as the association of marital status with the risk of CVD, after adjustment for the same covariates. Finally, we applied mediation analysis methods to assess the mediating effect of LTL on the association between marital status and CVD.[34] We assumed that covariates measured at the same time as exposure suffice to adjust for confounding for the associations between exposure and outcome, between mediator and outcome, and between exposure and mediator.

In the secondary analysis, we further adjusted the association between marital status and CVD and the mediation analysis for physical activity, smoking, diabetes, hypertension and dyslipidemia, to assess whether the results of the main analysis could be attributable to these factors.

Cluster-robust standard errors were used to correct for the dependence between co-twins. Proportional hazards assumption was justified based on Schoenfeld residual tests. We used time since blood sample collection as the underlying timescale. All analyses were performed for the entire population and also for men and women separately. Because LTL was not measured for all participants of SALT, the association of marital status with CVD as noted in the main analysis might not pertain to the entire cohort of SALT. We therefore performed an additional analysis to examine the association of marital status with CVD in entire cohort of SALT. Further, although within-twin analysis better controls for potential residual confounding, there is a possibility of over-matching in within-twin analysis by potentially also adjusting for possible mediators.[35] As the primary aim of the present study was to assess the role of telomeres as a potential mediator linking together marital status and CVD, we did not perform within-twin comparison in our main analysis. In a sensitivity analysis, however, we performed a within-twin analysis to assess the impact of residual confounding due to shared and unmeasured common factors within a twin pair.

Statistical analyses were performed using SAS V.9.4 and R V.3.5 (R Foundation for Statistical Computing, Vienna, Austria) with *survival* package.

All participants gave informed consent. We did not involve patients or the public in our work.

Table 3 Association between leucocyte telomere length and risk of cardiovascular disease

	Men (HR (95% CI))	Women (HR (95% CI))	Total (HR (95% CI))
Per SD increase	0.74 (0.59 to 0.92)	0.86 (0.66 to 1.12)	0.79 (0.66 to 0.93)
Categorical variable by tertiles			
(0.18, 0.94]	Ref	Ref	Ref
(0.94, 1.17]	1.02 (0.90 to 1.16)	1.02 (0.85 to 1.21)	1.02 (0.92 to 1.13)
(1.17, 2.08]	0.82 (0.71 to 0.96)	0.96 (0.80 to 1.16)	0.88 (0.78 to 0.99)

Models adjusted for marital status, age, sex, educational attainment and body mass index.

No patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

Among the 10 058 participants who were included in the analysis, mean age at interview was 58.8 years (SD 7.8) and 48.1% (N=4833) were men. Married or cohabiting participants comprised 79.8% (N=8024) of the study cohort. A total of 2010 participants had an incident CVD diagnosis during a median follow-up of 9.8 years. Other characteristics are described in table 1.

Table 2 reports the association of marital status with LTL. Compared with individuals who were married or cohabiting, people who were divorced or separated (β: −0.014, 95% CI: −0.035, 0.007), widowed (β: −0.035, 95% CI: −0.061, 0.010), or living alone (β: −0.033, 95% CI: −0.052, 0.014) had shorter LTL after multivariable adjustment. As a group, individuals who were living singly, regardless of reason, had a shorter LTL (β: −0.027, 95% CI: −0.040, 0.014) than individuals who were married or cohabiting. One SD increase of LTL was associated with a lower risk of CVD (HR: 0.79, 95% CI: 0.66, 0.93) (table 3). Compared with LTL below the lowest tertile, LTL above the highest tertile was also associated with a lower risk of CVD (HR: 0.88, 95% CI: 0.78, 0.99).

Being divorced or separated, widowed, or living alone were all associated with a higher hazard of CVD. When comparing the individuals who were living singly, regardless of reason, with the individuals who were married or cohabiting, the adjusted HR (95% CI) was 1.21 (1.08, 1.35). Analyses stratified by sex yielded similar estimates (table 4).

In the mediation analysis with additional adjustment for LTL, the HR for living singly, regardless of reason, remained unchanged compared with the result of main analysis, using individuals who were married or cohabitating as the reference (table 5).

In the secondary analysis, the association of marital status with risk of CVD attenuated but remained statistically significant,

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Table 4 Association between marital status and risk of cardiovascular disease (CVD)

	Men			Women			Total		
	CVD (n)	Person-years	HR (95% CI)	CVD (n)	Person-years	HR (95% CI)	CVD (n)	Person-years	HR (95% CI)
Marital status									
Married or cohabiting	1064	39 075.3	Ref	499	38 625.0	Ref	1563	77 700.3	Ref
Divorced or separated	79	2396.1	1.35 (1.07 to 1.70)	68	4227.0	1.18 (0.90 to 1.54)	147	6623.1	1.25 (1.05 to 1.49)
Widowed	47	998.2	1.01 (0.75 to 1.37)	96	3608.1	1.24 (0.99 to 1.55)	143	4606.3	1.14 (0.96 to 1.37)
Living alone	95	3479.7	1.26 (1.01 to 1.57)	62	4546.8	1.22 (0.93 to 1.59)	157	8026.5	1.22 (1.03 to 1.45)
Married or cohabiting	1064	39 075.3	Ref	499	38 625.0	Ref	1563	77 700.3	Ref
Living singly*	221	6874.0	1.22 (1.05 to 1.43)	226	12 381.8	1.22 (1.04 to 1.42)	447	19 255.8	1.21 (1.08 to 1.35)

Models adjusted for age, sex, educational attainment and body mass index.
*Living singly includes divorced or separated, widowed and living alone.

after additionally adjusting for smoking, physical activity, diabetes, hypertension and dyslipidemia (table 6). Similar change of the result was noted for the mediation analysis.

LTL was measured only in a subset of the study participants of SALT, and on average participants with LTL measurement were more likely married or cohabitating at baseline (78.7%) and had a lower risk of CVD during follow-up (incidence rate=1268.4 per 100 000 person-years) than participants without LTL measurement (70.0% and 1860.4 per 100 000 person-years; p values for difference <0.0001). In the sensitivity analysis of entire cohort of SALT, we found stronger association between marital status and CVD (online supplementary table 1), compared with the main analysis (p=0.07). The within-twin analysis provided also slightly stronger association (online supplementary table 1), compared with the main analysis, with however largely overlapping CIs (p=0.73).

DISCUSSION

In this cohort comprising more than 10 000 Swedish twins, we found that individuals living singly, regardless of reason, had shorter telomeres and a higher risk of CVD than individuals who were married or cohabiting. However, our data indicated a rather limited contribution, if any, of telomere shortening to the association between marital status and risk of CVD.

Our study is the first large-scale prospective cohort study assessing the association between marital status and TL. In a cross-sectional study involving 321 participants from South Carolina, USA, people who were married or living with a partner were shown to have a longer LTL (T/S ratio: 1.69) than their unmarried counterparts (T/S ratio: 1.59).[16] Another cross-sectional study of 298 residents in Taiwan also found the married individuals to have a longer LTL than the widowed ones.[18] The largest study published so far was the Health and Retirement Study in which 3526 individuals had salivary telomeres assessed. People who were separated or divorced were shown to have shorter salivary telomeres than people who were continuously married, after adjusting for demographic and socioeconomic variables, lifestyles and other stressful life events.[17] Our study is the largest until now with findings corroborating the previous reports. These results altogether contribute to the mounting evidence that marital status is indeed associated with TL.

Our findings confirm the results of previous investigations that living singly is associated with increased risk of CVD. For example, the risk of MI was shown higher among divorced individuals than the married ones in the Health and Retirement Study.[36] In the Million Women Study, individuals living without a partner had a higher risk of ischaemic heart disease than those living with a partner.[37] A recent meta-analysis summarising all available evidence showed that the risk of coronary heart disease was 16% higher among the unmarried than the married individuals,[2] although null results have also been reported elsewhere.[38] The potential mechanisms underlying the link between marital status and CVD are yet entirely clear. The prevailing hypotheses have so far centred on socioeconomic and behavioural aspects, as well as cardio-metabolic regulations.[5–7 10] Additional adjustment for potential lifestyle and health consequences of marital status in the present study, including physical activity, smoking, hypertension, diabetes and dyslipidemia, led to diminished magnitude of the association of marital status with CVD, corroborating therefore that health behaviours and metabolic disorders may indeed be potential mediating factors linking together marital status and CVD. In addition to these, other pathways might also exist. The end of marriage or loss of life partner can render high level of perceived stress, which may lead to dysregulated immune function and inflammatory processes, and increase vulnerability to CVD.[2 39] Biological ageing, including telomere shortening, oxidative stress, etc, is another determinant for cardiovascular health, which perturbs

Table 5 Adjustment for leucocyte telomere length (LTL) for the association between marital status and risk of cardiovascular disease

	Men (HR (95% CI))	Women (HR (95% CI))	Total (HR (95% CI))
Multivariable adjusted model*			
Marital status			
Married or cohabiting	Ref	Ref	Ref
Living singly†	1.22 (1.05 to 1.43)	1.22 (1.04 to 1.42)	1.21 (1.08 to 1.35)
Additionally adjusted for LTL			
Marital status			
Married or cohabiting	Ref	Ref	Ref
Living singly†	1.22 (1.05 to 1.42)	1.21 (1.03 to 1.42)	1.20 (1.08 to 1.34)

*Models adjusted for age, sex, educational attainment and body mass index.
†Living singly includes divorced or separated, widowed and living alone.

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Table 6 Association between marital status and risk of cardiovascular disease with additional adjustment for smoking, physical activity, diabetes, hypertension and dyslipidemia

	Men (HR (95% CI))	Women (HR (95% CI))	Total (HR (95% CI))
Multivariable adjusted model*			
Marital status			
Married or cohabiting	Ref	Ref	Ref
Living singly†	1.15 (0.98 to 1.36)	1.12 (0.94 to 1.34)	1.12 (1.00 to 1.27)
Additionally adjusted for LTL			
Marital status			
Married or cohabiting	Ref	Ref	Ref
Living singly†	1.15 (0.97 to 1.35)	1.12 (0.93 to 1.34)	1.12 (1.00 to 1.26)

*Models adjusted for age, sex, educational attainment, body mass index, smoking, physical activity, diabetes, hypertension and dyslipidemia.
†Living singly includes divorced or separated, widowed and living alone.
LTL, leucocyte telomere length.

metabolic and haemodynamic mechanisms in the cardiovascular system, and induces abnormal changes in cells and tissues that accelerate cardiovascular dysfunction.[40] In this study, we made a novel effort to postulate that this link may in part be attributable to TL shortening, an established biomarker for biological ageing and a newly recognised correlate of psychological distress. However, because the association between marital status and CVD remained almost unchanged after additional adjustment for LTL, regardless of adjustment for physical activity, smoking, hypertension, diabetes and dyslipidemia, it seems unlikely that LTL plays a pivotal role in the association between marital status and CVD.

Major strengths of this study include the prospective cohort design, the large sample size and the complete follow-up spanning >16 years. The availability of a very large sample with LTL measurement is another strength. The use of LTL as a novel biomarker for the social and psychological aspects of health has been proposed previously.[15 41] However, due to the difficulties in collecting a large sample of LTL assessments with long enough follow-up time to identify a sufficient number of health outcomes, few studies have so far investigated LTL as a potential contributor to proposed associations between psychosocial factors and subsequent health outcomes. In this study, we took advantage of a large sample of Swedish twins with rich information on marital status and LTL measurements, and exploited the national health registers to identify incident CVD diagnoses. We are also the first to examine the role of LTL (as a biomarker of ageing and psychological distress) in the association of marital status with the subsequent risk of CVD. Potential limitations of the study include the fact that information on marital status, educational attainment, weight and height was self-reported, and prone to measurement error. Further, marital status and LTL were measured only once and LTL was measured using qPCR, leading to another possibility of misclassification. Because these potential misclassifications are not likely to be differential for individuals who developed CVD later on, they have most probably led to an under-estimation of the studied associations. Given that we only enrolled individuals born in Sweden in this study, whether our results are generalisable to individuals with different cultural and socio-economic background remains to be assessed. LTL was measured only in a subset of the study participants of SALT, and participants with LTL measurement were on average more likely married or cohabitating at baseline and had a lower risk of CVD during follow-up than participants without LTL measurement. Consequently, the association of marital status with CVD as noted in the present study is likely an underestimate of the same association in the entire cohort of SALT. We additionally conducted within-twin analyses to control for residual confounding due to shared and unmeasured factors within a twin pair. We found slightly stronger association between marital status and CVD in this analysis, compared with the results of the main analysis, but the difference was not statistically significant.

In summary, this large prospective cohort study demonstrated an association of marital status with LTL as well as the risk of CVD. The increased risk of CVD in relation to divorce, separation, widowhood, or living alone did however not seem to be attributable to shortening of LTL.

Key messages

What is already known on this subject?

- Marital status has been suggested as a risk factor for cardiovascular disease. The underlying mechanisms of this association were postulated to be through psychological distress and cardio-metabolic changes, whereas the potential role of other pathways, such as expedited ageing as a result of altered marital status, has however never been examined.

What might this study add?

- In this population-based cohort study that included more than 10 000 Swedish twins, there was good evidence showing that living singly, regardless of reason, was associated with a shorter leucocyte telomere length (an established biomarker of ageing) and a higher risk of cardiovascular disease. The study does however not support that telomere length shortening contributes greatly to the association between marital status and cardiovascular disease.

How might this impact on clinical practice?

- The association of marital status and cardiovascular disease is not mediated by shortened telomeres in this study population.

Contributors RC and FF conceived the study design. NP and SH collected the data. RC and YZ analysed the data. All authors contributed to the manuscript editing and provided comments and suggestions.

Funding The study was partially financed by the Karolinska Institutet (the Strategic Research Area in Epidemiology and the Senior Researcher Award to FF).

Competing interests None declared.

Patient consent for publication Not required.

Heart: first published as 10.1136/heartjnl-2019-315629 on 14 November 2019. Downloaded from http://heart.bmj.com/ on March 28, 2024 by guest. Protected by copyright.

Ethics approval This study was approved by the Regional Ethical Review Board in Stockholm.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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