



Reaction time and established risk factors for total and cardiovascular disease mortality: Comparison of effect estimates in the follow-up of a large, UK-wide, general-population based survey

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ABSTRACT

Higher cognitive function is associated with faster choice reaction time (CRT), and both are associated with a reduced risk of mortality from all-causes and cardiovascular disease (CVD). However, comparison of the predictive capacity of CRT, an emerging risk factor, with that for established 'classic' risk factors for mortality, such as smoking, hypertension or obesity, is lacking. The purpose of this study was to compare the relative impact of CRT with a range of established risk factors for all-cause and CVD mortality. The UK Health and Lifestyle Survey (HALS) is a national sample survey of adults in England, Scotland, and Wales. In 1984/85, data on lifestyle factors, socioeconomic status, and health were collected for 9003 individuals. CRT data were available for 7414 individuals. With different predictor variables having differing coding structures, we used the relative index of inequality (RII) to explore the relation of a range of risk factors with mortality by computing the risk in disadvantaged (high risk; e.g., smokers) relative to advantaged (low risk; e.g., non-smokers) persons. During an average of 20 years of follow-up, there were 1289 deaths (568 ascribed to CVD). In age- and sex-adjusted models in which all-cause mortality was the outcome of interest, CRT mean (RII = 2.57, 95% CI = 1.98, 3.33) was the second most important predictor of death after smoking (RII = 3.03, 95% CI = 2.45, 3.75). For death from CVD, CRT mean (RII = 2.31, 95% CI = 1.55, 3.43) was again the second most important risk factor for death, behind systolic blood pressure (RII = 4.37, 95% CI = 3.03, 6.29). These analyses suggest that CRT, a moderately high correlate of intelligence, is an important risk factor for death from all-causes and CVD.

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1. Introduction

There is a growing and evolving literature on the importance of intelligence as a risk factor for mortality. Lower cognitive test scores and greater cognitive decline, both in young and old age, have been associated with an increased risk of mortality (Shiple, Der, Taylor, & Deary, 2006; Shipley, Der, Taylor, & Deary, 2007; Deary, Whalley, & Starr, 2003; Osler et al., 2003). Using an Australian population

sample of 897 individuals aged over 70 years, Korten et al. (1999) found that poorer cognitive performance was associated with an increased risk of mortality over a 4 year follow-up. Smits, Deeg, Kriegsman and Schmand (1999) also reported that poorer cognition in old age (indexed by information processing speed and fluid intelligence) was a significant predictor of premature mortality over an average of 3.3 years of follow-up. Similar results have been found by other investigators (Anstey, Luszcz, Giles, & Andrews, 2001; Bassuk, Wypij, & Berkman, 2000) and also when cognition is measured in middle age (Pavlik et al., 2003; Shipley et al., 2006) and early life (Batty, Deary, & Gottfredson, 2007). However, studies using premorbid measures of intelligence (such as Batty et al., 2007) have a more solid methodological

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base than studies using middle or older aged samples. This is because adult diseases such as hypertension or cardiovascular disease are related to cognitive decline (Rafnsson, Deary, Smith, Whiteman, & Fowkes, 2007; Knopman et al., 2001). Therefore, the issue of reverse causality can hamper the interpretation of results when truly premorbid cognitive ability is not measured. In a systematic review, Batty et al. (2007) retrieved nine population based studies which linked premorbid intelligence with later mortality (Furu, Lindgarde, Ljung, Munck, & Kristenson, 1984; O'Toole, Adena, & Jones, 1988; Snowdon, Greiner, Kemper, Nanayakkara, & Mortimer, 1999; Whalley & Deary, 2001; Hart et al., 2003; Osler et al., 2003; Deary et al., 2004; Kuh, Richards, Hardy, Butterworth, & Wadsworth, 2004; Hemmingson, Melin, Allebeck, & Lundberg, 2006). All studies showed an inverse association between premorbid IQ and later mortality; that is, higher childhood IQ scores were associated with lower rates of mortality.

Although they are fewer in number, cognition-mortality studies have also examined specific causes of death and morbidity, such as cardiovascular disease (e.g. Batty et al., 2008a,b, Batty, Shipley, Mortensen, & Deary, 2009a, Batty et al., in 2009a; Shipley, Der, Taylor, & Deary, 2008). Using data from the Scottish Mental Survey 1932, Hart et al. (2003) found that lower childhood IQ was associated with an increased risk of CVD events even after controlling for a range of established CVD risk factors (smoking, blood pressure and lung function). Gale, Martyn and Cooper (1996) found that poor cognitive functioning was associated with nearly a three-fold increase in risk of death from stroke.

The studies described above used standardised psychometric measures of cognition. Such tests do not provide information on which specific cognitive domains might link individual differences in mental ability with health. Whalley and Deary (2001) suggested that cognition may be linked with health because mental ability may be a proxy for aspects of bodily integrity and/or efficiency of information processing. Following this hypothesis, recent studies are using cognitive measures such reaction time tests, which attempt to capture these more basic fundamental indicators of the brain's information processing efficiency. Their items are simple and identical and they afford the derivation of timed estimates of subjects' processing efficiency and consistency. Furthermore, standard psychometric cognitive ability test scores and measures of speed of information processing, such as reaction time, are moderately highly correlated (Deary, Der, & Ford, 2001). Deary and Der (2005) found that, when psychometric intelligence and reaction time were entered as predictors in a multivariate cognition-mortality analysis, only reaction time made a significant independent contribution to mortality. This indicates that the relatively simple index of reaction time might account for the effect of IQ on mortality. Within the mortality literature, using the sample described in the present study, Shipley et al. (2006) found that slower and more variable simple and choice reaction times were significantly related to an increased risk of all-cause mortality over 19 years of follow-up. Furthermore, Shipley et al. (2008) found that slower and more variable reaction times were significantly associated with a higher risk of death from cardiovascular disease, stroke, and respiratory disease after controlling for age and sex. In addition, Shipley et al. (2008) tested a reverse causality explanation by excluding deaths in

the first five years after reaction time measurement, and repeating their analyses: there was very little attenuation of reaction time's effects on mortality.

Whereas there is a growing evidence that reaction time is positively related to mortality experience, there has been no comparison between reaction time as a potentially new risk factor and other very well established risk factors for mortality—particularly CVD—such as smoking, hypertension or obesity. Chockalingam and Balaguer-Vinto (1999) have suggested that these well established risk factors may explain only 50% of the variance in CVD. This shortfall may be due to sub-optimal measurement of the classic risk factors (Yusuf, Reddy, Ounpuu, & Anand, 2001), or the failure to capture emerging risk factors, of which cognitive performance, including reaction time, may be one. Moreover, it is valuable in itself to know how strongly reaction time is associated with mortality by comparison with well-established risk factors.

The current study examined the relative influence of reaction time, and other established risk factors for CVD and all-cause mortality (Yusuf et al., 2001) using data from the mortality follow-up of the Health and Lifestyle Survey, a large, UK-wide, general-population based survey.

2. Method

2.1. Subjects

Subjects were members of the Health and Lifestyle Survey (HALS), a nationwide sample survey of all adults resident in England, Scotland and Wales (Cox et al., 1987). In 1984/85, 12,254 addresses were randomly selected from electoral registers, and one adult from each household aged 18 years and over was invited to take part in the baseline questionnaire interview (Blaxter, 1987). Of the 12,254, 9003 agreed and were eligible to enter the study and completed the initial interview. On comparing this sample to the 1981 census it can be concluded that the HALS participants are representative of the general population (Blaxter, 1987). Due to a large number of individuals not completing the second part of the baseline assessment ($N = 1589$), physical measurements and measures of reaction time were completed on 7414 of the 9003 participants. A further 842 individuals did not return the self-completion booklet, giving a maximum sample size of 6572.

2.2. Procedure

Information for the baseline data was collected during two home visits (Cox et al., 1987). The first was completed by a trained interviewer who collected questionnaire information on home and family circumstances, educational attainment, self-reported health, health attitudes, and health behaviours. The second home visit was completed by a nurse who completed a physiological examination involving measures of height, weight, girth, blood pressure, pulse rate, and respiratory function. Tests of reaction time were also administered at this stage (Huppert, 1987).

2.3. Reaction time

Reaction time was assessed using a portable, battery-operated device which consisted of a small LCD screen and

five buttons numbered 1, 2, 0, 3, and 4 from left to right (Shipley et al., 2006). The box can produce a number of scores including simple reaction time mean, simple reaction time standard deviation, four-choice reaction time mean and four-choice reaction time standard deviation. Only four-choice reaction time mean (CRT mean) was used in this study (only for correct responses). CRT mean was the time taken to press one of four keys corresponding to the presentation of one of four digits (1–4). Eight practice trials were followed by forty test trials. Inter-stimulus interval varied between 1 and 3 s. The same device has been used in other population-based surveys (Deary and Der, 2005).

2.4. Adult risk factors

The behavioural risk factors were self-reported (Shipley et al., 2006; Blaxter, 1987). Current smoking status was recorded as: never smoked, ex-smoker, current light smoker, current medium smoker and current heavy smoker. A light smoker was defined as smoking less than ten cigarettes per day, a medium smoker was defined as smoking between ten and nineteen cigarettes per day, and a heavy smoker was defined as smoking twenty or more cigarettes per day. Level of alcohol consumption per week was measured in alcohol units. One unit of alcohol was equivalent to half a pint of beer or cider, or a single measure of spirits, or a glass of wine, or a small glass of fortified wine. Participation in various types of vigorous and non-vigorous physical activities was recorded. Activities included work-associated physical activity, week day and weekend walking, housework, gardening, home improvement, and involvement in a range of sports activities. Duration in minutes was recorded for each activity. This information was summed to produce a summary variable indicating minutes spent doing activity.

The physical health variables were measured by a nurse. For resting heart rate, four recordings of pulse rate were taken at one minute intervals and measured in beats per minute. Median pulse rate was calculated. Four serial recordings of blood pressure (BP) were made at one minute intervals using an “Accutorr” automatic blood pressure measuring instrument. Median systolic blood pressure values were computed. To correct for anti-hypertensive medication—such that persons on treatment will have a lowered blood pressure—the method of “addition of a simple constant” was used (Tobin, Sheehan, Scurrah, & Burton, 2005). Thus, 10 mmHg was added to treated systolic BP measurements in those who were currently taking BP lowering medication. Diastolic blood pressure was not included in the analysis due to the high correlation between systolic and diastolic blood pressure values in this sample ($r=0.86$, $p<0.0001$). Waist/hip ratio was calculated by dividing girth at waist in centimetres by hip size in centimetres. Body mass index (kg/m^2) (BMI) was calculated using standard formulae ($\text{weight}/[\text{height}]^2$) as based on height, measured in metres, using a portable stadiometer, and weight in kilograms using electronic scales.

The General Health Questionnaire (GHQ-30), a measure of psychological distress, was completed by the participants at home and returned by post. Each of the 30 questions in the GHQ were answered using a four-point Likert scale noting the degree to which the respondent has experienced a particular symptom (‘not at all’, ‘no more than usual’, ‘rather more than

usual’, ‘much more than usual’). Scoring was then based on the 1, 2, 3, 4 method, where ‘not at all’ is scored as 1, ‘no more than usual’ is scored as 2, ‘rather more than usual’ is scored as 3, and ‘much more than usual’ is scored as 4. This produces a total score ranging from 30 to 120. The higher the score on the GHQ-30, the higher the distress.

2.5. Covariates

The socioeconomic status covariates were all self-reported. Occupational social class was derived using the Registrar General's occupational social class and based on the current occupation of the head of household, or usual occupation if the head of household was retired or unemployed. It comprised six categories: professional (I), managerial (II), skilled non-manual (IIIN), skilled manual (IIIM), semi-skilled manual (IV), and unskilled (V). Education was recorded as the highest qualification obtained by the participant either while at school or since school. This variable had five levels: first or higher degree; semi-professional or professional qualification, for example nursing or teaching qualifications; A-level or equivalent, including advanced City and Guilds certificates; O-level or equivalent, including ordinary City and Guilds certificates; no educational qualifications (work-related certificates were included in this category). Income was recorded as the total monthly household income after tax but including any benefits, pensions, or other income received. The variable had 12 levels: less than £110; £110–£230; £231–£340; £341–£415; £416–£580; £581–£750; £751–£830; £831–£995; £996–£1250; £1251–£1500; £1501–£2080; £2081 or more.

2.6. Vital status

Deaths of HALS participants are continually notified by the United Kingdom's National Health Service central registry which also provided copies of death certificates. The data are periodically updated with the information provided and the data used here comprise the latest available update of June 2005. Death certificates contained information on up to three primary and two secondary causes of death coded according to the Ninth International Classification of Diseases (World Health Organisation, 1975). For the present analysis a single “underlying cause” of death was used. Two sets of analyses were completed, first for death from all-causes and second for death from cardiovascular disease (CVD) (ICD9 codes 390–459).

2.7. Analyses

In the mortality analyses, survival time was age at death or age at June 2005 for surviving participants. Cox's proportional hazards regression, as implemented in the SAS Version 9.1 Phreg procedure (SAS Institute Inc., 1999), was used to derive hazard ratios with accompanying 95% confidence intervals.

As RT and the risk factors are all measured on different scales, in order to facilitate comparison of their effects on total and CVD mortality we computed the relative index of inequality (RII) (Hayes & Berry, 2002; Mackenbach & Kunst, 1997; Sergeant & Firth, 2006). To do this we first scored each risk factor variable so that higher values reflected greater disadvantage. Thus, for physical activity the scores were

Table 1

Relative index of inequality (95% CI) for the relation of RT and established risk factors with all-cause mortality.

All-cause mortality (1289 deaths/ 5066 participants)	Adjustments			
	Age and sex		Age, sex, social class, education, income	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Smoking	3.03 (2.45, 3.75)	<0.0001	2.66 (2.15, 3.30)	<0.0001
CRT mean	2.57 (1.98, 3.33)	<0.0001	1.95 (1.49, 2.56)	<0.0001
Physical activity	1.78 (1.48, 2.13)	<0.0001	1.74 (1.45, 2.08)	<0.0001
Systolic blood pressure	1.63 (1.32, 2.03)	<0.0001	1.60 (1.29, 1.98)	<0.0001
Resting heart rate	1.59 (1.33, 1.90)	<0.0001	1.55 (1.29, 1.85)	<0.0001
GHQ-30	1.53 (1.25, 1.86)	<0.0001	1.38 (1.13, 1.69)	0.001
Waist/hip ratio	1.22 (1.01, 1.48)	0.04	1.25 (1.04, 1.51)	0.02
Alcohol	1.05 (0.85, 1.29)	0.66	1.21 (0.98, 1.50)	0.07
BMI	0.95 (0.78, 1.15)	0.59	0.92 (0.76, 1.11)	0.36

reversed. Then the subjects were ranked on each risk factor variable and the ranks divided by the sample size. For continuous variables this recoding yields values with a range of $1/N$ to 1, which is effectively 0 to 1 with the large sample employed here. For grouped data, the subjects in each group were assigned the mid-rank of that group, again divided by the sample size. So, for example, a hypothetical grouped variable where bottom and top groups each contain ten percent of the subjects would have the value 0.05 assigned to the bottom group and 0.95 to the top group.

These recoded variables were used as the predictors in the cox regressions. As the hazard ratios from cox regression represent the proportionate difference in the hazards for a 1 point difference in the predictor; and as the recoded risk factor variables have a range of 0 to 1, the resulting hazard ratios give the mortality risk for the most disadvantaged relative to the most advantaged (e.g., the longest CRT relative to the shortest, or the highest blood pressure relative to the lowest). Their interpretation is the same as a relative risk: if the RII hazard ratio is 1.40 then the mortality risk of the most disadvantaged is 40% higher than that of the most advantaged, whereas a RII hazard ratio of 1.00 would indicate no elevated risk, that is, a null relationship. It is worth noting that, since grouped data have a range of less than 1, the RII hazard ratios are larger than estimates based on contrasts of the top and bottom groups would be.

We produced two separate models for each risk factor: in the first, we adjusted for age and sex; in the second, we adjusted for age, sex, and markers of socioeconomic position (social class, education and income). The mortality analyses were completed both for death from all-causes and death from CVD.

3. Results

Only participants who had complete data for choice reaction time, age, sex, social class, educational attainment, income, alcohol consumption, smoking status, physical activity, blood pressure, BMI, resting heart rate, waist/hip ratio, and GHQ-30 were included in the analysis. The final sample consisted of 5066 (2329 men, 2737 women) participants with complete data out of a possible 6572. Mean age of the sample was 46.0 years ($SD = 16.5$) with a range of 18–

94 years. Between July 1985 and June 2005, 1289 of the 5066 participants had died from all-causes (702 men, 587 women) and 568 had died from CVD (313 men, 255 women). Mean age of those who died was 64.1 years ($SD = 11.8$). Just over half the sample had no formal educational qualifications (52.3%) and just over a quarter had reached O-level or equivalent (26.3%). The majority of the sample belonged to Registrar General group II (managerial—23.5%) and IIM (skilled manual—36.6%). Correspondingly, around half of the sample (58%) had a monthly total household income that fell between £751–£830 and £1251–£1500.

3.1. All-cause mortality

We previously reported (Shipley et al., 2006) a significant positive association between CRT mean and risk of death from all-causes after controlling for age and sex ($RII = 2.57$, 95% $CI = 1.98, 3.33$; Table 1). Here, smoking was the only risk factor which showed a larger risk of death ($RII = 3.03$, 95% $CI = 2.45, 3.75$) than choice reaction time. The remaining risk factors were ordered due to size of risk as: physical activity ($RII = 1.78$, 95% $CI = 1.48, 2.13$), systolic blood pressure ($RII = 1.63$, 95% $CI = 1.32, 2.03$), resting heart rate ($RII = 1.59$, 95% $CI = 1.33, 1.90$), GHQ-30 ($RII = 1.53$, 95% $CI = 1.25, 1.86$), and waist/hip ratio ($RII = 1.22$, 95% $CI = 1.01, 1.48$). Alcohol consumption and BMI showed no significant associations with risk of death from all-causes. After adding social class, education, and income to the model the ordering of the risk factors did not change, although some modest attenuation was seen for all statistically significant risk factors.

3.2. CVD mortality

CRT mean ($RII = 2.31$, 95% $CI = 1.55, 3.43$; Table 2) was the second most important risk factor for death from CVD after controlling for age and sex. The most important risk factor for death from CVD was systolic blood pressure ($RII = 4.37$, 95% $CI = 3.03, 6.29$). Other significant risk factors for death from CVD were smoking ($RII = 1.85$, 95% $CI = 1.34, 2.56$), physical activity ($RII = 1.74$, 95% $CI = 1.32, 2.29$), GHQ-30 ($RII = 1.46$, 95% $CI = 1.09, 1.97$), BMI ($RII = 1.43$, 95% $CI = 1.06, 1.92$), and resting heart rate ($RII = 1.32$, 95% $CI = 1.01, 1.73$). After further adjustment for socioeconomic status, the importance of CRT

Table 2

Relative index of inequality (95% CI) for the relation of RT and established risk factors with CVD mortality.

CVD mortality (568 deaths/ 5066 participants)	Adjustments			
	Age and sex		Age, sex, social class, education, income	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Systolic blood pressure	4.37 (3.03, 6.29)	<0.0001	4.26 (2.96, 6.13)	<0.0001
CRT mean	2.31 (1.55, 3.43)	<0.0001	1.83 (1.21, 2.77)	0.004
Smoking	1.85 (1.34, 2.56)	0.0002	1.63 (1.18, 2.27)	0.003
Physical activity	1.74 (1.32, 2.29)	<0.0001	1.70 (1.30, 2.24)	0.0001
GHQ-30	1.46 (1.09, 1.97)	0.01	1.36 (1.01, 1.83)	0.04
BMI	1.43 (1.06, 1.92)	0.02	1.39 (1.04, 1.86)	0.03
Resting heart rate	1.32 (1.01, 1.73)	0.04	1.30 (0.99, 1.70)	0.05
Waist/hip ratio	1.26 (0.95, 1.68)	0.10	1.29 (0.98, 1.71)	0.07
Alcohol	0.88 (0.64, 1.21)	0.43	1.00 (0.72, 1.38)	0.99

mean (RII = 1.83, 95% CI = 1.21, 2.77) for risk of death from CVD remained the second most important risk factor. The ordering of the remaining risk factors did not change substantially and, for most variables, including CRT, the attenuation of the effects was small to modest.

4. Discussion

The aim of this study was to examine the relative effect of choice reaction time mean compared to a number of established risk factors for death from all-causes and CVD. This is a significant contribution to cognitive epidemiology because, for the first time, it quantifies the contribution of CRT and mortality alongside risk factors that lay and medical professional people have, for several decades, regard as important and substantial. Smoking and CRT mean were the two most important risk factors for death from all-causes, while systolic blood pressure and CRT mean were the two major risk factors for death from CVD. For total mortality, CRT mean and smoking showed almost equal risk. However, for CVD, risk of death in those with higher systolic blood pressure was nearly double that of those with a slower CRT.

Poor (longer) reaction time and other indices of cognitive performance have been related to an increased risk of mortality (Batty et al., 2007; Batty & Deary, 2004; Whalley et al., 2001; Osler et al., 2003; Pavlik et al., 2003; Deary & Der, 2005; Shipley et al., 2006), including death from CVD and stroke (Shipley et al., 2008). However, within the cognition-health literature few have made reference to the comparability of the risk of low cognition to more established mortality risk factors. In a study examining the mental ability-all cause mortality association in a Scottish cohort, Deary and Der (2005) stated in their discussion that, "Here we found that psychometric intelligence and reaction times were significantly related to survival over the next 14 years, with an effect size comparable to that of smoking status." The present study has been able to quantify this statement and has shown that smoking, blood pressure and CRT mean are the most important risk factors for all-cause and CVD mortality.

4.1. Plausible mechanisms

There are several explanations for how some classic risk factors are related to death from CVD. For example, physical inactivity or a poor diet can lead to obesity which raises levels of triglycerides, blood pressure and blood glucose, and lowers HDL-cholesterol, while smoking and alcohol have a direct effect on the development of CVD. So what might explain the association between CRT mean and mortality, particularly from CVD? Several mechanisms have been proposed for the association between cognitive ability and mortality more broadly (Batty et al., 2007; Deary & Der, 2005; Gottfredson & Deary, 2004). Firstly, cognitive function may be an indicator of lifecourse insults including living conditions and illness (Whalley & Deary, 2001). For example, studies have shown a negative association between cognition and diseases such as diabetes (Awad et al., 2004) and atherosclerosis (Gale et al., 2008) which are known risk factors for mortality. Furthermore, previous studies on cognition and mortality have shown that controlling for socioeconomic status variables such as social class and education do not greatly attenuate the association between

mental ability and death (Shipley et al., 2006; Deary & Der, 2005). Therefore, the association cannot fully be explained by the fact that higher cognitive ability is associated with more favourable social circumstances and in turn better health (Hart et al., 2003). The same argument can be used for health behaviour variables such as smoking and alcohol consumption (Hart et al., 2003; Batty et al., 2008a,b), and also with disease and injury management. Thus, higher intelligence is associated with lower levels of smoking and alcohol consumption and better management of personal healthcare. However, these hypotheses link general cognition to mortality and not reaction time.

Amongst the theories proposed for a relationship between cognition and mortality, any of which may in fact be true, is the hypothesis focusing on system integrity. Whalley and Deary (2001) hypothesised that reaction time, as a measure of speed of the brain's information processing capacity, may be a proxy marker for bodily system integrity. This way, slower reaction times, or poorer information processing ability, might be an indication of suboptimal physiological functioning (Deary & Der, 2005) which in turn may be related to early death.

4.2. Study strengths and weaknesses

The HALS has a number of advantages for investigating risk factors for mortality. First, the study group consists of a UK wide population-based sample of adults of all ages. This not only provides good statistical power but the results can be applied to the general population. Second, HALS has a wide range of data available which allows for the comparison of a number of established risk factors for mortality against cognition. Thirdly, the measure of cognition in HALS (reaction time) has been shown to be a good measure of the underlying processes of cognition, namely information processing (Deary et al., 2001; Deary & Der, 2005). However, HALS was not designed to be a CVD risk factors survey and no blood samples were taken so there is no information on risk factors such as blood glucose and lipids.

In conclusion, in the first study of its kind, we found that choice reaction time mean compared favourably with established risk factors for total and CVD mortality. Indeed, it was one of the more powerful risk factors in the present study.

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