Anaemia and physical and mental health in the very old: An individual participant data meta-analysis of four longitudinal studies of ageing

ABSTRACT

Objective. To determine the physical and mental health of very old people (aged 80+) with anaemia.

Methods. Individual level meta-analysis from five cohorts of octogenarians (n=2,392): *[NZ study]* Māori, *[NZ study]* non-Māori, *[NL study]*, *[UK study]*, and *[JP study]*. Mixed models of change in functional ability, cognitive function, depressive symptoms, and self-rated health over time were separately fitted for each cohort. We combined individual cohort estimates of differences according to the presence of anaemia at baseline, adjusting for age at entry, sex, and time elapsed. Combined estimates are presented as differences in standard deviation units (i.e., standardised mean differences–SMDs).

Results. The combined prevalence of anaemia was 30.2%. Throughout follow-up, participants with anaemia, on average, had: worse functional ability (SMD -0.42 of a standard deviation across cohorts; CI -0.59,-0.25); worse cognitive scores (SMD -0.27; CI -0.39,-0.15); worse depression scores (SMD -0.20; CI -0.31,-0.08); and lower ratings of their own health (SMD -0.36; CI -0.47,-0.25). Differential rates of change observed were: larger declines in functional ability for those with anaemia (SMD -0.12 over five years; CI -0.21,-0.03) and smaller mean difference in depression scores over time between those with and without anaemia (SMD 0.18 over five years; CI 0.05,0.30).

Conclusion. Anaemia in the very old is a common condition associated with worse functional ability, cognitive function, depressive symptoms, and self-rated health, and a more rapid decline in functional ability over time. The question remains as to whether anaemia

itself contributes to worse outcomes or is simply a marker of chronic diseases and nutrient deficiencies.

253 words

INTRODUCTION

Anaemia is a common condition in older people. Globally, the prevalence of anaemia in the older population is estimated to be 24% [1], but there is evidence suggesting that the prevalence is much higher at more advanced ages [2, 3]. Recent population projections estimate a three-fold increase in the number of older persons aged 80 years and over worldwide from 2019 to 2050 [4], which underlines the importance of ascertaining the impact of common health conditions over time in later life.

Studies have demonstrated that variability in the older population's health status and quality of life increases with age [5-8]. In the general older population, anaemia is associated with poorer functional status [9-12]; worse cognitive function [10, 13, 14]; and depressive symptoms [12, 15, 16]. A few studies have also shown that older people's haemoglobin levels are positively associated with self-rated health (SRH) [17, 18]. Less is known as to whether these adverse outcomes are also observed in the very old.

Towards Understanding Longitudinal Investigations of older People (TULIP) Consortium is an international collaboration of investigators from four longitudinal studies of health and well-being in advanced age (persons aged 80 years and over). Using data from these studies provides the opportunity to combine individual-level data for increased statistical power. In this analysis, we aim to determine whether anaemia – regardless of its causes – is longitudinally associated with worse functional status, cognitive impairment, depressive symptoms, and poorer SRH.

METHODS

This is a meta-analysis of individual-level data provided by five cohorts of older people from the four studies that are part of the TULIP Consortium: (1) *[NZ study]*; (2) the *[NL study]*; (3) the *[UK study]*; and (4) the *[JP study]*.

The *[NZ study]* sample consisted of 937 age-eligible older people living in areas within the geographic boundaries of the Bay of Plenty and Lakes District Health Boards in New Zealand. In 2010, 421 were Māori participants aged 80 to 90 years and 516 were non-Māori participants aged 85 years. Māori people, the indigenous people of New Zealand, are presented as a distinct cohort. In the *[NL study]*, 599 residents of the city of Leiden, Netherlands, who reached the age of 85 between September 1997 to September 1999 were enrolled in the study. The *[UK study]* recruited 1,042 older primary care patients who turned 85 years old in 2006 and were registered in participating general practices in the Newcastle and North Tyneside Primary Care Trusts in the UK. The *[JP study]* study sample consisted of 542 randomly selected participants aged 85 years and over in March 2008, who were residing in the Shinjuku, Minato, and Shibuya wards in Tokyo, Japan. All studies had appropriate ethics approval from their respective authorities. Participants from these five cohorts who consented to blood sample collection and had available haemoglobin values at baseline provided the data for the present analysis: 551 (58.8%) of the total *[NZ study]* sample; 555 (92.7%) of the *[NL study]*; 752 (72.2%) of the *[UK study]*; and 534 (98.5%) of *[JP study]*.

The measures and methods of data collection by the four TULIP Consortium studies have been previously reported [19-22]. Information on variables used for the present analysis are summarised in Supplementary Material 1.

Determinant

We used the World Health Organization (WHO) criteria [23] for anaemia (females with haemoglobin values of <120mg/dl and males with haemoglobin values <130mg/dl) to categorise participants as anaemic or non-anaemic at baseline.

Measures of physical and mental health

Six waves of data on functional ability, cognitive function, depressive symptoms, and SRH were available from *[NZ study]* and the *[NL study]*, which were obtained from assessments performed at baseline and every year after up to five years. In the *[UK study]*, the five waves of outcome data were collected at baseline, 1.5, 3, 5, and 10 years. *[JP study]* provided data at baseline, on 3-year follow-up, and on 6-year follow-up.

Measures of functional ability were Nottingham Extended Activities of Daily Living (NEADL) in *[NZ study]*; Groningen Activity Restriction Scale (GARS) in the *[NL study]*; sum of 17 items on activities of daily living in the *[UK study]*; and Lawton Instrumental Activities of Daily Living (IADL) in *[JP study]*. Cognitive function was assessed using the Modified Mini-Mental State (3MS) examination in *[NZ study]* and the Mini-Mental State Examination (MMSE) in other studies. In *[NZ study]*, the *[NL study]*, and the *[UK study]*, depressive symptoms were assessed by the 15-item Geriatric Depression Scale (GDS-15); in *[JP study]*, it was the WHO (five) Well-being Index (WHO-5). As for SRH, there were some

differences in the item wording and response categories of the four studies (details provided in Supplementary Material 1).

Analysis

For each of the five cohorts, descriptive statistics of age, sex, comorbidities, and frequency of anaemia are presented in Table 1; baseline characteristics with respect of functional ability, cognitive function, depressive symptoms, and SRH are shown in Table 2. Unadjusted change in baseline status was examined by fitting mixed models of change in outcomes over time with measurement occasions as level 1 units, participants as level 2 units, and years elapsed since baseline added as a fixed predictor and as a random slope at the participant level (i.e., a random coefficient model) separately for each cohort. If the random slope model was too complex given number of observations available we stepped back to a simpler random effect specification [24]. For models with measures of functional ability, cognitive function, and number of depressive symptoms as dependent variables, linear mixed models were fitted; these models yield a difference in mean score. Cumulative link mixed models were fitted for models of SRH; this model yields a difference in log odds which we exponentiated into an odds ratio (Table 2).

Building on the unadjusted change models described above, sequential models were fitted to estimate: (1) the physical and mental health of participants with and without anaemia throughout the follow-up period (mean score difference models) and (2) rates of change in physical and mental health over time (differential change models). Mean score difference models compare the outcomes of participants with and without anaemia under the assumption that rates of change in outcomes are similar whether or not anaemia is present, whereas

differential change models allows the rate of change in outcomes to differ between those with and without anaemia.

The mean score difference between participants with and without anaemia was examined by adding the presence of anaemia at baseline to the unadjusted change models described above and adjusting for age at entry to the study and sex (Figure 1). Estimates obtained from these mean score difference models were transformed into standardised mean differences (SMDs) – the regression coefficient for anaemia in standard deviation (SD) units – and pooled by random effects meta-analysis. We reversed the polarity of estimates where higher scores indicate poorer outcomes so that SMDs will have a negative sign when participants with anaemia are worse off than those without anaemia. Interval estimates were obtained to a 95% level of confidence.

We added the interaction term for baseline anaemia*years elapsed since baseline to the mean score difference models described above to assess the differential rate of change over time in outcomes (differential change models) according to the presence of anaemia at baseline. Using a previously described method for calculating effect size in longitudinal studies [25], the total difference in change over five years was obtained by multiplying the interaction term estimate by the time period of interest. The resulting estimate was then standardised and pooled to a rate differential (Figure 1).

The differential change models described above were used to predict scores on functional ability, cognitive function, and number of depressive symptoms, and probabilities of providing a high SRH (i.e., selecting either of the two best response options). The resulting

predictions were used to create a graphical representation of the overall difference in outcomes according to the presence of anaemia, which take into account overall mean differences in outcomes and differential rate of change in outcomes over time (Supplementary Material 2).

R was used to perform data analysis.

RESULTS

A total of 2,392 participants with haemoglobin values at baseline were included in the analysis (Table 1). Median age of the combined sample was 85.0 years (IQR 85.0, 85.9); 59.2% of participants were female; 46.3% had cardiovascular disease; 16.5% had diabetes; 19.2% had cancer; and 30.2% were anaemic at baseline. Measures of functional ability, cognitive function, number of depressive symptoms, and SRH at baseline and unadjusted mean changes per year are reported in Table 2.

Anaemia and physical and mental health throughout follow-up

Figure 1 summarises differences in outcomes between participants with and without anaemia after adjusting for age at recruitment, sex, and time elapsed since baseline, where a negative sign in the SMD indicates that participants with anaemia are worse off than participants who were not anaemic. SMDs from individual cohorts were consistently negative across outcomes, but the magnitude of differences varied across cohorts.

Throughout follow-up across the five cohorts, participants who were anaemic at baseline had functional ability scores that were -0.42 of an SD (CI -0.59 to -0.25) from the scores of their non-anaemic counterparts (combined SMD from Figure 1a). Figure 1b shows that the cognitive function scores of those with and without anaemia differed by -0.27 SDs across cohorts (CI -0.39 to -0.15). Participants with anaemia also had more depressive symptoms than those without anaemia (Figure 1c, -0.20 SDs across cohorts, CI -0.31 to -0.08). As for SRH, those with anaemia had a lower odds of selecting a higher SRH category than those without anaemia: the combined SMD of -0.36 (CI -0.47 to -0.25) in Figure 1d is equivalent to a combined OR of 0.52 (CI 0.44 to 0.61).

Anaemia and rates of change in physical and mental health over time

When interactions were explored to show differential rates of change over time between participants with and without anaemia, there were larger declines in functional ability scores for those with anaemia (rate differential from Figure 1a, -0.12 SDs over five years across cohorts, CI -0.21 to -0.03) and a smaller mean difference in depression scores was observed over five years (Figure 1c, 0.18 SDs across cohorts, CI 0.05 to 0.30). Patterns of change were not significantly different for cognitive function and SRH. As shown in the graphical representation of the overall difference in outcomes (initial difference plus rate differential) according to the presence of anaemia (Supplementary Material 2), the interaction contribution to the difference between those with and without anaemia was minimal.

DISCUSSION

We investigated whether anaemia in the very old, regardless of causes, is associated with adverse physical and mental health outcomes using data from five cohorts of older people in

advanced age. Overall, we found that participants with anaemia had worse functional ability, cognitive function, depressive symptoms, and SRH throughout follow-up, and were observed to have a more rapid decline in functional ability over time.

Throughout follow-up, participants with anaemia were worse off than their non-anaemic counterparts in all the outcomes examined in the present study. This is consistent with previous work on the general older population that found associations between anaemia and poorer functional status [9-12], worse cognitive function [10, 13, 14], depression [12, 15, 16], and lower SRH [17, 18] – most of which are limited to cross-sectional analyses. We further add to the literature on the physical and mental health outcomes of anaemia over time by demonstrating differential rates of change in functional ability and depressive symptoms according to the presence of anaemia at baseline. The question remains as to whether anaemia itself contributes to the differences observed such as more rapid decline in functional ability over time or it simply serves as a marker of underlying chronic diseases and nutrient deficiencies. Renal impairment, for example, may often contribute to anaemia, but does not appear to be prevalent in most cohorts included in this analysis [26-29]. As for depression, which is characterised by fluctuations in symptoms over time even in later life [30-32], potential adjustment between mood and health status over time, being treated for depression, the tendency for depression to ease in advanced age, and the ability of very old people to maintain their quality of life despite considerable morbidity may have contributed to the smaller mean difference in depressive symptoms over time that we observed between those with anaemia and those without.

In our study, anaemia was a common condition and a predictor of worse outcomes. However, the magnitude of differences in outcomes, including rates of change over time, was relatively small – the largest being half a standard deviation in any measure of functional ability. The clinical significance of this finding could be debated, particularly in the context of invasiveness of diagnostic tests for anaemia (e.g., bone marrow aspiration, endoscopy) when its aetiology remains unexplained after initial investigations [33-35]; the risks associated with therapeutic modalities (e.g., erythropoiesis-stimulating agents, iron supplementation) [33-36]; and issues of treatment efficacy in the older population [36]. Furthermore, it remains unclear whether these relatively small differences in outcomes will be observed after accounting for the impact of chronic diseases and nutrient deficiencies. Although comparing specific causes of anaemia was beyond the scope of the present analysis, this could have also shed some light regarding the disproportionately higher anaemia prevalence in *[JP study]*, and thus should be examined in future research. Another consideration is that the association between levels of haemoglobin may not be linear. Prior studies suggest that the risk for poor outcomes according to haemoglobin levels follows a U-shaped pattern in older people. For example, the odds of reporting mobility difficulties [37] and rates of cognitive decline [38] were lowest at mid-normal (i.e., around 140 mg/dl). It is possible that our dichotomisation to anaemic and non-anaemic may have masked such associations. In addition, sequential blood tests were only available in some cohorts. We therefore only examined how anaemia at baseline would influence outcomes over time, potentially underestimating associations related to concurrent anaemia or change in anaemia status.

A key strength of the present study is the use of individual level data from five cohorts of older people in advanced age, which made it possible to examine longitudinal associations between anaemia and our outcomes. Transforming unstandardised estimates from individual

cohorts into SMDs is another key strength, as this allowed us to calculate a combined effect size rather than taking a narrative approach to synthesising findings from the five cohorts. Although stronger inferences may be drawn from the present analysis due to the application of longitudinal, meta-analytic techniques, we are unable to establish causality from this observational study. Another limitation is that we may have introduced selection bias because we can only include the subset of participants who consented to blood sample collection in the analysis. The relative consistency of estimates from individual cohorts is, however, reassuring. Areas for future inquiry include examination of optimal mid-normal haemoglobin values in the very old; the physical and mental health outcomes of current anaemia status or change in anaemia status; and the impact of anaemia over and above that of chronic diseases and nutrient deficiencies.

Conclusion

Overall, anaemia in the very old was associated with worse functional ability, cognitive function, depressive symptoms, and SRH, and a predictor of more rapid decline in functional ability over time. Clinical interpretation remains unclear – an important question to address is whether anaemia itself independently contributes to worse outcomes at advanced ages or it is simply a marker of underlying chronic diseases and nutrient deficiencies.

TABLE 1
Characteristics of participants with haemoglobin values at baseline of the five TULIP Consortium cohorts

Study	*[NZ study]* Māori (n=201)	*[NZ study]* non-Māori (n=350)	*[NL study]* (n=555)	*[UK study]* (n=752)	*[JP study]* (n=534)	Combined (n=2,392)
Age, med (IQR)	81.0 (80.0, 84.0)	85.0 (84.0, 85.0)	85.0 (85.0, 85.0)	85.5 (85.2, 85.8)	87.4 (86.3, 88.8)	85.0 (85.0, 85.9)
Female	112 (55.7)	178 (50.9)	368 (66.3)	456 (60.6)	301 (56.4)	1,415 (59.2)
Comorbidities						
Cardiovascular	141 (70.1)	233 (66.6)	230 (41.6)	390 (51.9)	113 (21.2)	1107 (46.3)
Diabetes	61 (30.3)	50 (14.3)	81 (14.7)	104 (13.8)	98 (18.4)	394 (16.5)
Cancer	40 (20.0)	172 (49.1)	98 (17.7)	48 (6.4)	100 (19.0)	458 (19.2)
Anaemia[a]	43 (21.4)	72 (20.6)	147 (26.5)	224 (29.8)	236 (44.2)	722 (30.2)
Mild anaemia[b]	33 (16.4)	54 (15.4)	112 (20.2)	155 (20.6)	172 (32.2)	526 (22.0)
Moderate anaemia[b]	10 (5.0)	18 (5.1)	33 (5.9)	66 (8.8)	61 (11.4)	188 (7.9)
Severe anaemia[b]	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.4)	3 (0.6)	8 (0.3)

[a] Using the WHO (2011) criteria for anaemia: females with haemoglobin <120mg/dl, males with haemoglobin <130mg/dl

[b] Anaemia severity defined using the WHO (2011) criteria: haemoglobin 110-119mg/dl in females and 110-129mg/dl in males as mild; 80-109 mg/dl as moderate for both sexes; and <80mg/dl as severe for both sexes

TABLE 2
Functional ability, cognitive function, depressive symptoms, and SRH at baseline and change in outcomes over time in the TULIP Consortium cohorts

	Measure [a]	Baseline Med (IQR)	Change over time [b,c] Estimate (CI)
Functional ability			
[NZ study] Māori	NEADL	19.0 (16.0, 20.3)	-0.35 (-0.51, -0.18)
[NZ study] non-Māori	NEADL	19.0 (17.0, 20.0)	-0.60 (-0.70, -0.49)
[NL study]	GARS [d]	28.0 (22.0, 40.0)	3.92 (3.63, 4.21)
[UK study]	Summed score [d]	3.0 (1.0, 7.0)	0.98 (0.90, 1.05)
[JP study]	IADL	5.0 (4.0, 5.0)	-0.27 (-0.30, -0.23)
Cognitive function			
[NZ study] Māori	3MS	92.0 (86.1, 96.0)	-0.55 (-1.06, -0.03)
[NZ study] non-Māori	3MS	95.0 (90.4, 97.3)	-0.53 (-0.80, -0.26)
[NL study]	MMSE	26.0 (22.0, 28.0)	-0.96 (-1.08, -0.85)
[UK study]	MMSE	28.0 (25.0, 29.0)	-0.73 (-0.84, -0.62)
[JP study]	MMSE	27.0 (25.0, 29.0)	-0.35 (-0.47,-0.24)
Depressive symptoms			
[NZ study] Māori	GDS-15 [d]	2.0 (1.0, 3.0)	-0.03 (-0.11, 0.04)
[NZ study] non-Māori	GDS-15 [d]	2.0 (1.0, 3.0)	0.00 (-0.04, 0.05)
[NL study]	GDS-15 [d]	2.0 (1.0, 3.0)	0.37 (0.29, 0.45)
[UK study]	GDS-15 [d]	3.0 (2.0, 5.0)	0.29 (0.25, 0.33)
[JP study]	WHO-5	19.0 (15.0, 22.0)	-0.33 (-0.45 , -0.20)
SRH			
[NZ study] Māori	SRH	82 (40.8%) [e]	1.01 (0.91, 1.13) [f]
[NZ study] non-Māori	SRH	147 (42.1%) [e]	0.89 (0.81, 0.97) [f]
[NL study]	SRH	119 (21.7%) [e]	0.70 (0.65, 0.75) [f]
[UK study]	SRH	303 (41.2%) [e]	0.97 (0.93, 1.02) [f]
[JP study]	SRH	269 (51.2%) [e]	0.83 (0.76, 0.90) [f]

[a] NEADL – Nottingham Extended Activities of Daily Living, GARS – Groningen Activity Restriction Scale, IADL – Instrumental Activities of Daily Living, 3MS – Modified Mini-Mental State, MMSE – Mini-Mental State Examination, GDS-15 – 15-item Geriatric Depression Scale, WHO-5 – WHO (five) Well-being Index, SRH – Self-rated Health

[b] Ascertained by fitting a model with time elapsed since baseline as fixed and random effects, yields the average difference in score per year (or difference in log odds per year for SRH)

[c] Follow-up period was 5 years for *[NZ study]* and the *[NL study]*, 6 years for *[JP study]*, and 10 years for the *[UK study]*

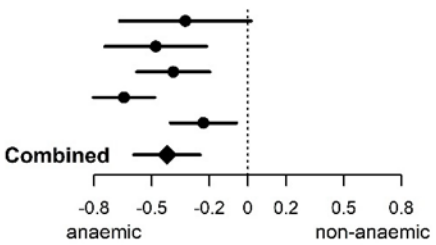
[d] Higher GARS score, higher summed disability score, and higher GDS-15 score all represent worse outcomes

[e] Number and proportion of participants who selected either of the two best SRH categories

[f] Odds ratio for selecting a higher SRH category after one year

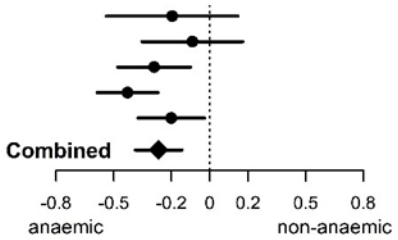
1a. Functional ability

Study	Measure[a]	N, Anaemia freq (%)	SD[b]	Unstandardised difference (CI)[c]	SMD (CI)[d]
[NZ study] Māori	NEADL	195, 42 (21.5%)	3.9	-1.25 (-2.52, 0.01)	-0.33 (-0.67, 0.02)
[NZ study] non-Māori	NEADL	345, 70 (20.3%)	3.3	-1.54 (-2.47, -0.62)	-0.48 (-0.74, -0.21)
[NL study]	GARS	554, 147 (26.5%)	14.1	5.39 (2.79, 7.99)[e]	-0.39 (-0.58, -0.20)
[UK study]	Summed score	749, 223 (29.8%)	4.5	2.81 (2.15, 3.48)[e]	-0.64 (-0.80, -0.48)
[JP study]	IADL	530, 234 (44.2%)	1.1	-0.26 (-0.44, -0.07)	-0.23 (-0.40, -0.06)
				Combined	-0.42 (-0.59, -0.25)
				-0.8 -0.5 -0.2 0 0.2 0.5 0.8	Rate differential[f]
				anaemic non-anaemic	-0.12 (-0.21, -0.03)



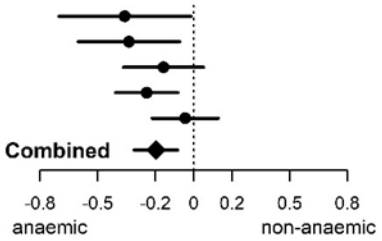
1b. Cognition

Study	Measure[a]	N, Anaemia freq (%)	SD[b]	Unstandardised difference (CI)[c]	SMD (CI)[d]
[NZ study] Māori	3MS	195, 42 (21.5%)	9.8	-1.92 (-4.86, 1.02)	-0.20 (-0.54, 0.15)
[NZ study] non-Māori	3MS	344, 70 (20.3%)	8.6	-0.78 (-3.06, 1.50)	-0.09 (-0.35, 0.17)
[NL study]	MMSE	555, 147 (26.5%)	6.3	-1.80 (-2.95, -0.65)	-0.29 (-0.48, -0.10)
[UK study]	MMSE	752, 224 (29.8%)	4.9	-2.06 (-2.81, -1.32)	-0.43 (-0.59, -0.27)
[JP study]	MMSE	527, 232 (44.0%)	3.8	-0.76 (-1.40, -0.11)	-0.20 (-0.37, -0.03)
				Combined	-0.27 (-0.39, -0.15)
				-0.8 -0.5 -0.2 0 0.2 0.5 0.8	Rate differential[f]
				anaemic non-anaemic	-0.05 (-0.22, 0.11)



1c. Depression

Study	Measure[a]	N, Anaemia freq (%)	SD[b]	Unstandardised difference (CI)[c]	SMD (CI)[d]
[NZ study] Māori	GDS-15	195, 42 (21.5%)	1.9	0.68 (0.06, 1.29)[e]	-0.36 (-0.70, -0.02)
[NZ study] non-Māori	GDS-15	345, 70 (20.3%)	1.9	0.63 (0.17, 1.10)[e]	-0.34 (-0.60, -0.07)
[NL study]	GDS-15	477, 119 (24.9%)	2.5	0.39 (-0.11, 0.88)[e]	-0.16 (-0.37, 0.05)
[UK study]	GDS-15	715, 206 (28.8%)	2.6	0.63 (0.28, 0.98)[e]	-0.25 (-0.41, -0.08)
[JP study]	WHO-5	526, 232 (44.1%)	5.3	-0.24 (-1.09, 0.61)	-0.04 (-0.22, 0.13)
				Combined	-0.20 (-0.31, -0.08)
				-0.8 -0.5 -0.2 0 0.2 0.5 0.8	Rate differential[f]
				anaemic non-anaemic	0.18 (0.05, 0.30)



1d. Well-being

Study	Measure[a]	N, Anaemia freq (%)	High SRH[g]	Odds ratio (CI)[h]	SMD (CI)[d]
[NZ study] Māori	SRH	201, 43 (21.4%)	82 (40.8%)	0.38 (0.18, 0.81)	-0.53 (-0.94, -0.12)
[NZ study] non-Māori	SRH	350, 72 (20.6%)	147 (42.1%)	0.41 (0.21, 0.80)	-0.49 (-0.87, -0.12)
[NL study]	SRH	551, 146 (26.5%)	119 (21.7%)	0.57 (0.37, 0.90)	-0.31 (-0.55, -0.06)
[UK study]	SRH	740, 217 (29.3%)	303 (41.2%)	0.46 (0.32, 0.66)	-0.43 (-0.64, -0.23)
[JP study]	SRH	529, 234 (44.2%)	269 (51.2%)	0.62 (0.44, 0.86)	-0.26 (-0.45, -0.08)
				Combined	-0.36 (-0.47, -0.25)
				-0.8 -0.5 -0.2 0 0.2 0.5 0.8	Rate differential[f]
				anaemic non-anaemic	0.10 (-0.04, 0.25)

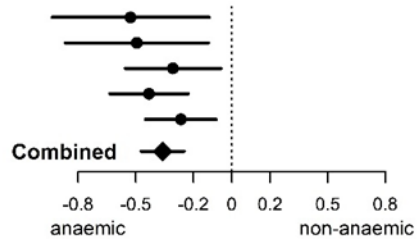


FIGURE 1
Difference over time in functional ability (1a), cognitive function (1b), depressive symptoms (1c), and well-being (1d) according to the presence of anaemia at baseline, adjusted for age at entry to the study, sex, and time elapsed since baseline, in the TULIP Consortium cohorts

[a] NEADL – Nottingham Extended Activities of Daily Living, GARS – Groningen Activity Restriction Scale, IADL – Instrumental Activities of Daily Living, 3MS – Modified Mini-Mental State, MMSE – Mini-Mental State Examination, GDS-15 – 15-item Geriatric Depression Scale, WHO-5 – WHO (five) Well-being Index, SRH – Self-rated Health

[b] Standard deviation of scores at baseline

[c] Difference in mean measure scores between participants with and without anaemia

[d] SMD – standardised mean difference, that is, the unstandardised difference in mean measure scores expressed in SD units; reversed polarity of estimates for GARS, summed disability score, and GDS-15 so that negative estimates consistently represent worse outcomes in participants with anaemia

[e] Higher GARS score, higher summed disability score, and higher GDS-15 score all represent worse outcomes

[f] Standardised differential rate of change over five years between participants with and without anaemia; ascertained by adding the interaction term for baseline anaemia*years elapsed since baseline to the model

[g] Selecting either of the two best SRH response options at baseline: excellent and very good in *[NZ study]*, *[NL study]*, and *[UK study]*, or very good and good in *[JP study]*

[h] Compares the odds for selecting a higher SRH category in participants with anaemia to those without anaemia

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