Appendices to the Article, "Iron deficiency without anaemia is a potential cause of fatigue: meta-analyses of randomised controlled trials and cross-sectional studies"

by Katsuhiko Yokoi and Aki Konomi

Appendix A

Formulae for the conversion of the test statistics

Table A-1 shows the formulae for the conversion of the test statistics. In univariate analyses, small sample bias was corrected because the considered studies included a study with a total sample size less than 50. In multivariate analysis, small sample bias was not corrected because the total sample sizes in the considered studies were more than 50 and small sample bias was negligible.

Table A-1. Formulae for the conversion of the test statistics into effect sizes (d) and their standard errors (σ_d) for the respective study design.

Reported data*	Effect size (d)	Standard error (σ_d)
Continuous data (sample sizes and probability) n_1, n_2, P	$\boldsymbol{c}(n_1+n_2-2)\left\{\left\|\boldsymbol{t}\left(\frac{P}{2}, n_1+n_2-2\right)\right\| \Big/ \sqrt{\frac{n_1 n_2}{n_1+n_2}}\right\}$	$\sqrt{\frac{1}{n_1}+\frac{1}{n_2}+\frac{d^2}{2(n_1+n_2)}}$
Continuous data (sample sizes, means and standard deviations) n_1, n_2, m_1, m_2, σ_1, σ_2	$\boldsymbol{c}(n_1+n_2-2)\left\{(m_1-m_2) \Big/ \sqrt{\frac{(n_1-1)\sigma_1^2+(n_2-1)\sigma_2^2}{n_1+n_2-2}}\right\}$	$\sqrt{\frac{1}{n_1}+\frac{1}{n_2}+\frac{d^2}{2(n_1+n_2)}}$
Dichotomous data (sample sizes for ordinary 2x2 contingency table)† h, i, j, k	$0.607\ \boldsymbol{ln}\left(\frac{\left(h+\frac{1}{2}\right)\left(k+\frac{1}{2}\right)}{\left(i+\frac{1}{2}\right)\left(j+\frac{1}{2}\right)}\right)$	$0.607\sqrt{\frac{(h+i+1)(h+i+2)}{(h+i)(h+1)(i+1)}+\frac{(j+k+1)(j+k+2)}{(j+k)(j+1)(k+1)}}$
Dichotomous data (sample sizes and fitting rates to the criteria in the ordinary 2x2 contingency table)† n_1, n_2, r_1, r_2	$0.607\ \boldsymbol{ln}\left(\frac{\left(n_1 r_1+\frac{1}{2}\right)\left\{n_2(1-r_2)+\frac{1}{2}\right\}}{\left\{n_1(1-r_1)+\frac{1}{2}\right\}\left(n_2 r_2+\frac{1}{2}\right)}\right)$	$0.607\sqrt{\frac{(n_1+1)(n_1+2)}{n_1(n_1 r_1+1)\{n_1(1-r_1)+1\}}+\frac{(n_2+1)(n_2+2)}{n_2(n_2 r_2+1)\{n_2(1-r_2)+1\}}}$
Dichotomous data (matched pairs for crossover design) u, v, w, x	$0.607\ \boldsymbol{ln}\left(\frac{\left(v+\frac{1}{2}\right)}{\left(w+\frac{1}{2}\right)}\right)$	$0.607\sqrt{\frac{(v+w+1)(v+w+2)}{(v+w)(v+1)(w+1)}}$
Multivariate linear regression n, q, ρ	$\frac{2\rho}{\sqrt{1-\rho^2}}$	$\frac{4}{(n-q)(1-\rho^2)}$
Multivariate logistic regression OR, SE_{LOR}	$0.607\ \boldsymbol{ln}(OR)$	$0.607\ SE_{LOR}$

*Explanation of variables

$\boldsymbol{c}(m)$: the correction factor for small sample bias by Hedges[27]. The formula is as follows.

$$\boldsymbol{c}(m) = 1 - \frac{3}{4m - 1}$$

d : the effect size

σ_d : the standard error for the effect size

P : the two-tailed probability

$\boldsymbol{t}(p, \omega)$: Student's t value for the one-tailed probability p and the degree of freedom ω

n_1 and n_2: group sizes for two groups 1 and 2

m_1 and m_2: means for two groups 1 and 2

σ_1 and σ_2: standard deviations for two groups 1 and 2

r_1 and r_2: fitting rates to the criteria for two groups 1 and 2

$\boldsymbol{ln}(y)$: the natural logarithm of y

n: total sample size

q: the number of independent variables

ρ: the correlation coefficient derived from the P value for the specified variable corresponding to Fe deficiency shown below

$$\rho = \pm\sqrt{\boldsymbol{t}\left(\frac{P}{2}, n - q - 1\right)^2 \Big/ \left\{\boldsymbol{t}\left(\frac{P}{2}, n - q - 1\right)^2 + (n - q - 1)\right\}},$$

where a plus or minus sign was given depending on the plus or minus sign of the regression coefficient

OR: the odds ratio for the variable corresponding to Fe deficiency

SE_{LOR}: the standard error for the log odds ratio

$$SE_{LOR} = \frac{\left[\{\boldsymbol{ln}(OR) - B_L\} + \{B_U - \boldsymbol{ln}(OR)\}\right]/2}{\boldsymbol{\Phi}^{-1}\left[1 - (1 - 0.01\alpha)/2\right]}$$

B_L: the lower bound of the α% confidence interval

B_U: the upper bound of the α% confidence interval

$\boldsymbol{\Phi}^{-1}(z)$: the inverse of the standard normal cumulative distribution for the probability z

The lower decimal places were estimated from the round off number of OR, B_L and B_U reported in the original paper using the Solver add-in of Excel software, based on the condition:

$\boldsymbol{ln}(OR) - B_L = B_U - \boldsymbol{ln}(OR)$.

†Crossover design not using matched comparison is also included.

Appendix B

Monte Carlo simulation study for the corrected log odds and its standard error in the matched-pair design

Because Sanchez-Meca et al. did not attempt simulation for the matched-pair design[29], the simulation study was made as follows. A continuous random number from 0 to 1 was generated n times using Microsoft Excel 2003 Software. We recorded the number of times when the generated random number was smaller than the assumed success rate φ. If the number of the succeeded case was a, the failed case became $b = n - a$. We assumed φ as 17/27 and n as 27 in the Monte Carlo simulation with 10,000 trials. For each trial, odds ratio: a/b, log odds ratio: $\boldsymbol{ln}(a/b)$, variance: $1/a+1/b$, standard error (SE): $(1/a+1/b)^{0.5}$, Haldane's corrected odds ratio[30]: $(a+0.5)/(b+0.5)$, corrected log odds ratio[30]: $\boldsymbol{ln}[(a+0.5)/(b+0.5)]$, the corrected variance by Gart and Zweifel[31]: $\{(a+b+1)(a+b+2)\}/\{(a+b)(a+1)(b+1)\}$ and the corrected standard error by Gart and Zweifel[31]: $[\{(a+b+1)(a+b+2)\}/\{(a+b)(a+1)(b+1)\}]^{0.5}$ were calculated. Then, mean, median, maximum, minimum, skewness and kurtosis for all parameters were obtained. Haldane's log odds ratio[30], and the corrected variance and the standard error by Gart and Zweifel[31] were found to be good estimates of the true values (i.e., 0.531 of the log odds, 0.159 of the variance and 0.399 of the standard error). The mean values of uncorrected log odds, uncorrected variance and uncorrected standard error overestimated the true values.

Table B-1. Mean, median, maximum, minimum, skewness and kurtosis for selected parameters in the Monte Carlo simulation with 10,000 trials. The assumed success rate was 17/27 and a number of total cases in each trial was 27.

	Mean	Median	Max	Min	Skewness	Kurtosis
Odds ratio	1.902	1.700	12.500	0.421	2.401	12.687
Log odds ratio	0.552	0.531	2.526	-0.865	0.265	0.434
Variance	0.168	0.159	0.540	0.148	3.719	25.765
Standard error	0.408	0.399	0.735	0.385	2.850	13.963
Haldane's odds ratio[30]	1.843	1.667	10.200	0.436	2.043	8.843
Haldane's log odds ratio[30]	0.530	0.511	2.322	-0.830	0.225	0.340
Corrected variance by Gart and Zweifel[31]	0.159	0.152	0.386	0.143	3.000	15.433
Corrected standard error by Gart and Zweifel[31]	0.398	0.390	0.621	0.378	2.489	9.959

Appendix C

Fatigue scale, outcome and effect size in the randomised controlled trials

Table C-1. The randomised controlled trial by Beutler et al. (1960)[13]

Fatigue scale	Outcome				ES*	SE
	Both effective	Only Fe Effective	Only placebo effective	Both non-effective		
Relative effectiveness	0	17	10	2	0.310	0.237

Table C-2. The randomised controlled trial by Krayenbuehl et al. (2011)[15]

Fatigue scale	Outcome				ES*	SE
	Fe		Placebo			
	effective	non-effective	effective	non-effective		
SPI improvement	28	15	19	28	0.600	0.261
	Difference in means†	*P* value				
BFI	-0.4‡	0.07			0.384	0.213

Table C-3. The randomised controlled trial by Morrow et al. (1968)[17]

Fatigue scale	Outcome				ES*	SE
	Fe		Placebo			
	effective	non-effective	effective	non-effective		
Presence or absence of self-reported excessive tiredness	10	7	9	8	0.272	0.408

Table C-4. The randomised controlled trial by Vaucher et al. (2012)[16]

Fatigue scale	Outcome				ES*	SE
	Fe		Placebo			
	mean	SD	mean	SD		
CAPPS fatigue score	-12.2	10.2	-8.7	11.7	0.318	0.143
MAF global fatigue index	-16.2	11.8	-11.2	10.8	0.440	0.143
MAF severity index of fatigue	-3.6	2.5	-2.7	2.3	0.373	0.143

Table C-5. The randomised controlled trials by Verdon et al. (2003)[14]

Fatigue scale	Outcome				ES*	SE
	Fe		Placebo			
	mean	SD	mean	SD		
Visual analog scale	-1.82	1.7	-0.85	2.1	0.507	0.173

Table C-6. The randomised controlled trial by Waldvogel et al. (2012)[18]

Fatigue scale	Outcome		ES*	SE
	Difference in means†	*P* value		
Fatigue Severity Scale	-0.06	0.760	0.051	0.166
Visual analog scale	-0.15	0.697	0.064	0.166

ES, effect size; SPI, Short Performance Inventory questionnaire; CAPPS, Current and Past Psychological Scale; MAF, Multidimensional Assessment of Fatigue score; BFI, Brief Fatigue Inventory questionnaire. *When the sign was positive, Fe treatment was effective to reduce fatigue. †The mean value for Fe group minus the mean value for Placebo group. The negative value denotes a positive effect of Fe treatment. ‡The median value was given instead of the mean value not available in the article. The mean value is not used for the calculation of ES and SE.

Appendix D

Fatigue scale, outcome and effect size calculated from univariate analysis in the cross-sectional studies

Table D-1. The cross-sectional study by Beck et al. (2012)[24]

Fatigue scale	Item	Data format*	IDNA	non-ID	*P*	ES†	SE
MFSI-SF	Total fatigue	*n*, *p*	22	211	0.017	-0.537	0.225
	General fatigue	*n*, *p*	22	211	0.029	-0.491	0.225
	Mental fatigue	*n*, *p*	22	211	0.498	-0.152	0.224
	Physical fatigue	*n*, *p*	22	211	0.008	-0.597	0.226
	Emotional fatigue	*n*, *p*	22	211	0.401	-0.188	0.224

Table D-2. The cross-sectional study by Comin-Colet et al. (2013)[20]

Fatigue scale	Item	Data format*	IDNA	non-ID	ES†	SE
MLHF	Fatigue scored ≥4	*n* (rate%)	349(63%)	203(51%)	0.298	0.108

Table D-3. The cross-sectional study by Goldenberg et al. (2013)[23]

Fatigue scale	Item	Data format*	IDNA	non-ID	ES†	SE
MFI-20	Total fatigue scored ≥13	2x2 (fit/unfit)	19 / 20	86 / 105	0.090	0.211
	General fatigue	Mean±SD	12.0±4.9	11.7±4.5	0.065	0.176
	Mental fatigue	Mean±SD	9.4±3.2	8.1±3.5	0.375	0.176
	Physical fatigue	Mean±SD	8.8±3.6	9.4±4.0	-0.152	0.176

Table D-4. The cross-sectional study by Lasocki et al. (2014)[22]

Fatigue scale	Item	Data format*	IDNA	non-ID	*P*	ES†	SE
MFI-20	General fatigue	*n*, *p*	20	60	1.00	0.000	0.258
	Mental fatigue	*n*, *p*	20	60	0.05	0.509	0.261

Table D-5. The cross-sectional study by Piednoir et al. (2011)[19]

Fatigue scale	Item	Data format*	IDNA	non-ID	*P*	ES†	SE
MFI-20	General fatigue	*n*, *p*	37	63	0.50	0.139	0.207
	Mental fatigue	*n*, *p*	37	63	1.00	0.000	0.207
	Physical fatigue	*n*, *p*	37	63	0.50	0.139	0.207

Table D-6. The cross-sectional study by Sawada et al. (2014)[21]

Fatigue scale	Item	Data format*	IDNA	non-ID	ES†	SE
CMI-J	Fatigability	Mean±SD	1.6±1.4	0.9±1.3	0.514	0.251

ID, iron deficiency; IDNA, iron deficiency without anaemia; ES, effect size; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; MLHF, Minnesota Living with Heart Failure questionnaire; MFI-20, Multidimensional Fatigue Symptom Inventory-20 Items; CMI-J, Cornell Medical Index Japanese Version. *The data format '*n*, *p*' denotes that the sample sizes for the two groups and *P* value (two tails) are given in the following columns; the format '*n* (rate%)' denotes that sample size and the percentage of fatigue-positive subjects in the parentheses are given in the following columns. †The positive sign signifies that subjects in the IDNA group complained of more fatigue than those in the non-ID group.

Appendix E

Fatigue scale, outcome and effect size calculated from the multivariate analysis in the cross-sectional studies

Table E-1. The multivariate analysis of the study by Beck et al. (2012)[24]

Fatigue scale	Item	Model*	Sample size, *n*	Number of variables, *q*	Regression coefficient	*P*	ES†	SE
MFSI-SF	Total fatigue	Linear	233	12	-6.54	0.084	-0.234	0.135
	Physical fatigue	Linear	233	12	-1.61	0.037	-0.283	0.136

Table E-2. The multivariate analysis of the study by Comin-Colet et al. (2013)[20]

Fatigue scale	Item	Model*	Sample size, *n*	Number of variables, *q*	Standardised regression coefficient	*P*	ES†	SE
MLHF	Physical dimension score	Linear	552	21	0.12	0.010	0.108	0.087

Table E-3. The multivariate analysis of the study by Goldenberg et al. (2013)[23]

Fatigue scale	Item	Model*	Sample size, *n*	Number of variables, *q*	OR‡	95%CI lower‡	95%CI upper‡	ES†	SE
MFI-20	Presence of problematic fatigue (general fatigue ≥13)	Logistic	280§	5	1.125	0.577	2.194	0.072	0.207

Table E-4. The multivariate analysis of the study by Lasocki et al. (2014)[22]

Fatigue scale	Item	Model*	Sample size, *n*	Number of variables, *q*	Regression coefficient	*P*	ES†	SE
MFI-20	General fatigue	Linear	80	6	-2.12	0.068	-0.434	0.238
	Mental fatigue	Linear	80	6	3.19	0.012	0.603	0.243

ES, effect size; OR, odds ratio; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; MLHF, Minnesota Living with Heart Failure questionnaire; MFI-20, Multidimensional Fatigue Symptom Inventory-20 Items. *'Linear' denotes multivariate linear regression model; 'Logistic' denotes multivariate logistic regression model. †The positive sign denotes that Fe deficiency increases fatigue. ‡The OR, the lower bound and the upper bound of the 95%CI were originally shown as 1.1, 0.6 and 2.2 respectively. The lower decimal values were estimated according to the procedure shown in Appendix A. §The sample size was comprised of 50 anaemic and 230 non-anaemic subjects.