Online Supplement

Index

1

Supplementary Text. Network meta-analysis.

Network meta-analysis is a technique used in meta-analysis of randomised controlled trials to leverage indirect evidence. With this method, evidence from comparisons between exposures A vs B and B vs C may be used to estimate the comparison A vs C. In this manuscript, we used network meta-analysis to estimate relative risks comparing metabolically healthy vs unhealthy individuals within BMI categories, as shown in the Figure.

Inset Figure. Network meta-analysis approach to estimate within-stratum relative risk. MHL, metabolically healthy lean; MUL, metabolically unhealthy lean; MHOW, metabolically healthy overweight; MUOW, metabolically unhealthy overweight; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese.

Problem of estimating within stratum RR

	Lean	Overweight	Obese
Metabolically healthy	(a1) MHL	(b1) MHOW	(c1) MHO
Metabolically unhealthy	(a2) MUL	(b2) MUOW	(c2) MUO

Available:
a2 − a1
b1 − a1
b2 − a1
c1 − a1
c2 − a1

Unavailable:
b2 − b1
c2 − c1

Network meta-analysis

Study	Analysis	Reference	Comparison	OR	95% CI
Meigs 2006	1	MHL	MHOW	1.3	0.9 – 1.9
Meigs 2006	2	MHL	MUOW	2.1	1.4 – 3.2
Meigs 2006	NMA	MHOW	MUOW	1.6	0.9 – 2.8

Results obtained from network meta-analysis had very similar central estimates to the ones obtained from publications (n = 1, i.e. Hinnouho et al.) or from the authors (n = 8; see also Supplementary Table S1). The widths of confidence intervals were larger for network meta-analysis based estimates compared with those obtained by direct analysis.

2

Supplementary Table S1. Comparison of estimates obtained from authors versus those obtained by network meta-analysis.

PMID	Study	T2D risk in overweight obtained from authors, RR (95% CI)	T2D risk in overweight obtained by NMA, RR (95% CI)	T2D risk in obese obtained from authors, RR (95% CI)	T2D risk in obese obtained by NMA, RR (95% CI)
23034958	Bo 2012	3.5 (1.4 – 8.7) *	3.5 (0.4 – 31.4)	2.0 (0.7 – 5.9) *	2.0 (0.2 – 18.9)
24361070	Sung 2012	1.9 (1.3 – 2.9) *	1.9 (0.8 – 4.5)	2.9 (1.4 – 5.9) *	2.8 (0.9 – 8.3)
23559087	Soriguer 2013	6.1 (1.4 – 27.4) *	5.6 (0.6 – 51.8)	3.0 (1.1 – 8.4) *	2.5 (0.3 – 18.3)
24670711	Hinnouho 2014	2.6 (2.1 – 3.2) *	2.5 (1.8 – 3.4)	2.0 (1.4 – 2.8) *	2.1 (1.4 – 3.3)
25139886	Twig 2014	2.2 (1.7 – 2.7) *	2.2 (1.5 – 3.0)	2.1 (1.6 – 2.7) *	2.1 (1.4 – 3.0)
25155902	Jung 2014	5.5 (4.0 – 7.5) *	5.5 (3.2 – 9.4)	2.9 (1.8 – 4.9) *	2.9 (1.5 – 5.7)
25131796	Heianza 2014	4.0 (3.5 – 4.6) *	3.9 (3.0 – 5.0)	3.1 (2.3 – 4.0) *	3.0 (2.1 – 4.2)
24823457	Heianza 2014	4.3 (2.8 – 6.5) *	4.3 (2.3 – 8.0)	2.2 (1.0 – 4.8) *	2.1 (0.9 – 5.2)
24870949	Rhee 2013	5.2 (3.3 – 8.4) *	5.2 (2.2 – 12.7)	3.4 (1.5 – 8.1) *	3.4 (1.1 – 10.8)
16735483	Meigs 2006	Not available	6.1 (2.1 – 17.4) *	Not available	4.7 (1.5 – 14.7) *
20852030	Arnlöv 2011	Not available	2.2 (1.1 – 4.5) *	Not available	0.9 (0.3 – 2.6) *
23491523	Appleton 2013	Not available	5.1 (1.5 – 17.0) *	Not available	3.7 (1.2 – 11.6) *
22621338	Kim 2012	Not available	3.8 (2.1 – 7.0) *	Not available	3.9 (1.8 – 8.4) *
21609497	Hadaegh 2011 men	Not available	2.1 (1.0 – 4.7) *	Not available	1.6 (0.6 – 4.5) *
21609497	Hadaegh 2011 women	Not available	3.3 (1.3 – 8.4) *	Not available	5.7 (2.1 – 15.5) *
24661566	Bell 2014	Not available	5.8 (1.0 – 32.7) *	Not available	2.7 (0.5 – 15.4) *
24257907	Aung 2014	Not available	3.2 (1.4 – 7.4) *	Not available	2.8 (1.2 – 6.7) *

PMID, Pubmed identity; T2D, type 2 diabetes; RR, relative risk; CI, confidence interval; NMA, network meta-analysis.
*used for the main analysis

3

Supplementary Table S2. Main analysis results when the studies of Sung et al. or Rhee et al. were included in the meta-analysis instead of those of Jung et al.

Analysis	Reference Group	Individuals at risk / incident T2D, N / N	Comparison Group	Individuals at risk / incident T2D, N / N	RR_{T2D} (95% CI)	P-value	I-squared %
Sung et al. included	Metabolically Healthy Lean	46,320 / 753	Metabolically Unhealthy Lean	7,479 / 533	3.9 (2.9 – 5.2)	< 0.001	69.4
Sung et al. included	Metabolically Healthy Overweight	29,866 / 925	Metabolically Unhealthy Overweight	16,060 / 1,650	3.1 (2.5 – 3.8)	< 0.001	63.4
Sung et al. included	Metabolically Healthy Obese	5,395 / 323	Metabolically Unhealthy Obese	7,479 / 1,167	2.5 (2.1 – 3.0)	< 0.001	11.6
Rhee et al. included	Metabolically Healthy Lean	48,668 / 752	Metabolically Unhealthy Lean	7,521 / 520	4.1 (3.1 – 5.4)	< 0.001	69.5
Rhee et al. included	Metabolically Healthy Overweight	32,937 / 950	Metabolically Unhealthy Overweight	16,058 / 1,586	3.4 (2.7 – 4.1)	< 0.001	61.0
Rhee et al. included	Metabolically Healthy Obese	5,799 / 327	Metabolically Unhealthy Obese	7,721 / 1,162	2.5 (2.1 – 3.0)	< 0.001	13.9

T2D, type 2 diabetes; RR, relative risk; CI, confidence interval.

4

Supplementary Table S3. Definitions of metabolic health. The Table reports definitions used in the studies selected for full article review. In parentheses the number of studies using a given definition is reported.

Definition Category (n = 177)

- Metabolic syndrome *(n = 72)*
  - Adult Treatment Panel III criteria
  - Customised or modified criteria
  - International Diabetes Federation
  - Harmonised criteria

- Combination of metabolic syndrome with insulin resistance or other *(n = 54)*
  - Metabolic syndrome and insulin resistance
  - Metabolic syndrome, insulin resistance and C-reactive protein
  - Metabolic syndrome and C-reactive protein
  - Metabolic syndrome and medical history
  - Other

- Insulin resistance *(n = 37)*
  - Homeostatic model assessment – insulin resistance
  - Hyperinsulinaemic euglycaemic clamp
  - Other

- Cardiorespiratory fitness *(n = 4)*

- Miscellaneous *(n = 10)*

5

Supplementary Table S4. Relative risk of type 2 diabetes in different metabolic health and BMI categories compared with the metabolically healthy lean category.

Study	Metabolically Healthy Lean, RR (95% CI)	Metabolically Unhealthy Lean, RR (95% CI)	Metabolically Healthy Overweight, RR (95% CI)	Metabolically Unhealthy Overweight, RR (95% CI)	Metabolically Healthy Obese, RR (95% CI)	Metabolically Unhealthy Obese, RR (95% CI)
2006 Meigs J Clin Endocrinol Metab	Referent	4.0 (1.4 – 11.6)	1.1 (0.5 – 2.4)	6.8 (3.4 – 13.4)	2.2 (0.9 – 5.6)	10.3 (5.4 – 19.5)
2011 Arnlöv Diabetes Care	Referent	3.3 (1.4 – 7.8)	3.5 (2.3 – 5.4)	7.8 (4.4 – 13.6)	11.7 (4.9 – 28.2)	10.1 (5.2 – 19.5)
2013 Appleton Diabetes Care	Referent	2.3 (0.7 – 7.5)	0.9 (0.4 – 2.2)	4.5 (2.1 – 9.7)	2.1 (0.9 – 5.0)	7.8 (3.8 – 16.0)
2012 Kim Metab Syndr Relat Disord	Referent	7.3 (3.4 – 15.9)	2.6 (1.7 – 4.0)	10.1 (6.5 – 15.7)	4.3 (2.4 – 7.9)	16.7 (10.4 – 26.8)
2011 Hadaegh BMC Public Health – Men	Referent	3.1 (1.3 – 7.0)	1.6 (0.9 – 2.9)	3.4 (2.0 – 5.8)	3.6 (1.5 – 8.4)	5.7 (3.3 – 9.9)
2011 Hadaegh BMC Public Health – Women	Referent	8.8 (3.7 – 21.2)	2.3 (1.2 – 4.3)	7.7 (4.0 – 14.9)	2.2 (1.0 – 4.7)	12.6 (6.9 – 23.2)
2012 Bo Am J Clin Nutr	Referent	16.7 (3.5 – 79.7)	5.7 (1.1 – 28.5)	20.0 (4.7 – 85.0)	15.8 (2.8 – 88.3)	31.4 (7.4 – 133.6)
2013 Soriguer J Clin Endocrinol Metab	Referent	5.2 (0.8 – 34.9)	0.7 (0.1 – 3.6)	3.9 (0.9 – 17.0)	3.0 (0.7 – 12.4)	7.3 (1.8 – 29.2)
2014 Bell Obes Rev	Referent	9.9 (2.9 – 36.7)	2.9 (0.8 – 10.3)	16.7 (5.2 – 54.2)	8.6 (2.4 – 30.4)	23.5 (7.3 – 75.6)
2014 Hinnouho Eur Heart J	Referent	3.2 (2.5 – 4.1)	1.6 (1.2 – 2.0)	3.9 (3.2 – 4.8)	3.2 (2.3 – 4.5)	6.9 (5.4 – 8.8)
2014 Aung J Clin Endocrinol Metab	Referent	2.5 (1.1 – 5.6)	1.8 (1.0 – 3.4)	5.8 (3.2 – 10.4)	3.9 (2.0 – 7.4)	10.9 (6.2 – 19.2)
2014 Twig Diabetes Care	Referent	1.7 (1.2 – 2.4)	1.5 (1.2 – 2.0)	3.3 (2.6 – 4.2)	3.2 (2.4 – 4.4)	6.7 (5.3 – 8.5)
2014 Jung Obesity	Referent	3.8 (2.7 – 5.4)	1.6 (1.0 – 2.4)	8.6 (6.3 – 11.8)	6.4 (3.6 – 11.3)	18.7 (13.4 – 26.0)
2014 Heianza Obesity	Referent	4.7 (3.9 – 5.7)	2.0 (1.7 – 2.4)	7.9 (6.8 – 9.2)	4.7 (3.6 – 6.1)	13.9 (11.6 – 16.7)
2014 Heianza J Clin Endocrinol Metab	Referent	4.9 (3.2 – 7.4)	1.3 (0.8 – 2.2)	5.6 (3.8 – 8.3)	5.9 (2.8 – 12.5)	12.6 (7.9 – 20.3)
Meta-analysis - Random Effects Model	**Referent**	**4.0 (3.0 – 5.1)**	**1.8 (1.5 – 2.2)**	**6.2 (4.8 – 8.0)**	**4.1 (3.3 – 5.1)**	**10.9 (8.5 – 13.9)**

6

Page 37 of 67   **Diabetes Care**

Supplementary Table S5. Cumulative incidence of type 2 diabetes in metabolic health and body mass index categories after the exclusion of studies in East Asian populations.

BMI category	BMI category cumulative incidence at 5 years[a]	BMI category cumulative incidence at 10 years [a]	Risk category	Proportion of healthy or unhealthy individuals in each BMI category	Relative risk within BMI category	Risk category 5 year cumulative incidence (95% CI*)	Risk category 10 year cumulative incidence (95% CI*)
Lean	0.3 %	0.8 %	Metabolically Healthy Lean	0.87	1	0.2% (0.2 – 0.2%)	0.6% (0.5 – 0.7%)
			Metabolically Unhealthy Lean	0.13	3.6	0.7% (0.5 – 0.9%)	2.2% (1.7 – 2.8%)
Over weight	0.8 %	2.7 %	Metabolically Healthy Overweight	0.66	1	0.5% (0.5 – 0.6%)	1.7% (1.6 – 1.9%)
			Metabolically Unhealthy Overweight	0.34	2.5	1.3% (1.2 – 1.4%)	4.4% (4.1 – 4.7%)
Obese	1.8 %	5.9 %	Metabolically Healthy Obese	0.42	1	1.1% (0.9 – 1.3%)	3.5% (2.9 – 4.1%)
			Metabolically Unhealthy Obese	0.58	2.2	2.4% (2.2 – 2.6%)	7.7% (7.2 – 8.1%)

7

Supplementary Figure S1. Relative risk of type 2 diabetes in different metabolic health and BMI categories compared with the metabolically healthy lean category in adjusted analyses.
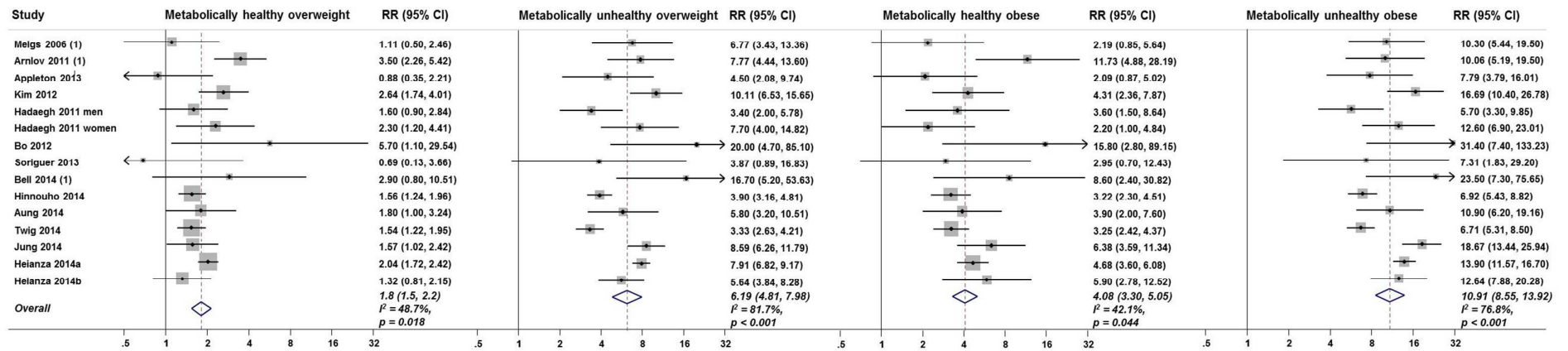
Supplementary Figure S2. Representative funnel plot indicating no publication bias for the meta-analysis of type 2 diabetes risk within obese. P-value from Egger's test = 0.53.

Funnel plot with pseudo 95% confidence limits

9
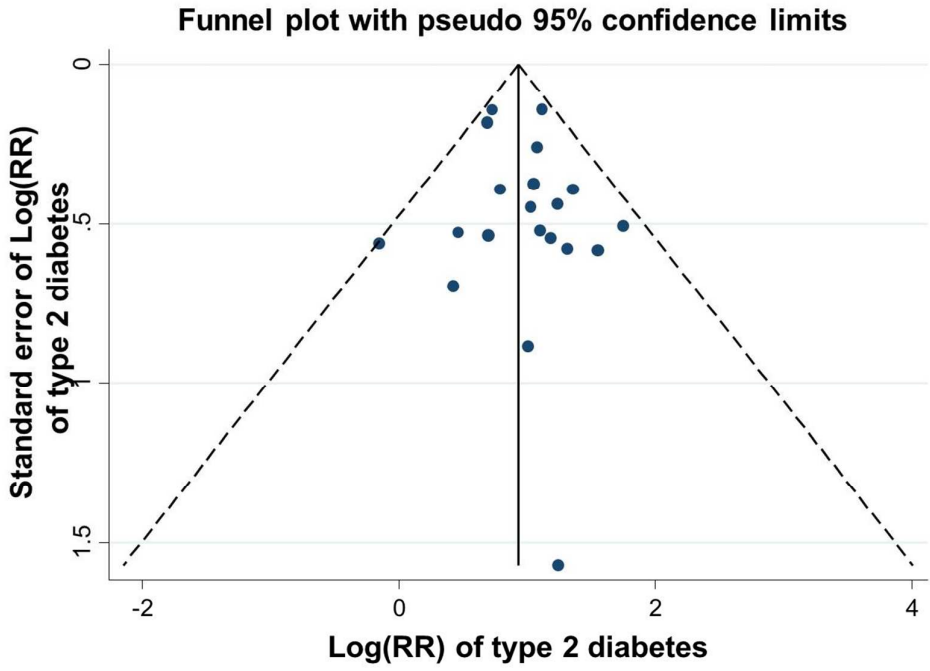
Supplementary Figure S3. Relative risk of type 2 diabetes in metabolically healthy vs unhealthy lean individuals in European and East Asian populations.