Supplementary Online Content

Feller M, Snel M, Moutzouri E, et al. Association of thyroid hormone therapy with quality of life and thyroid-related symptoms in patients with subclinical hypothyroidism: a systematic review and meta-analysis. *JAMA.* doi:10.1001/jama.2018.13770

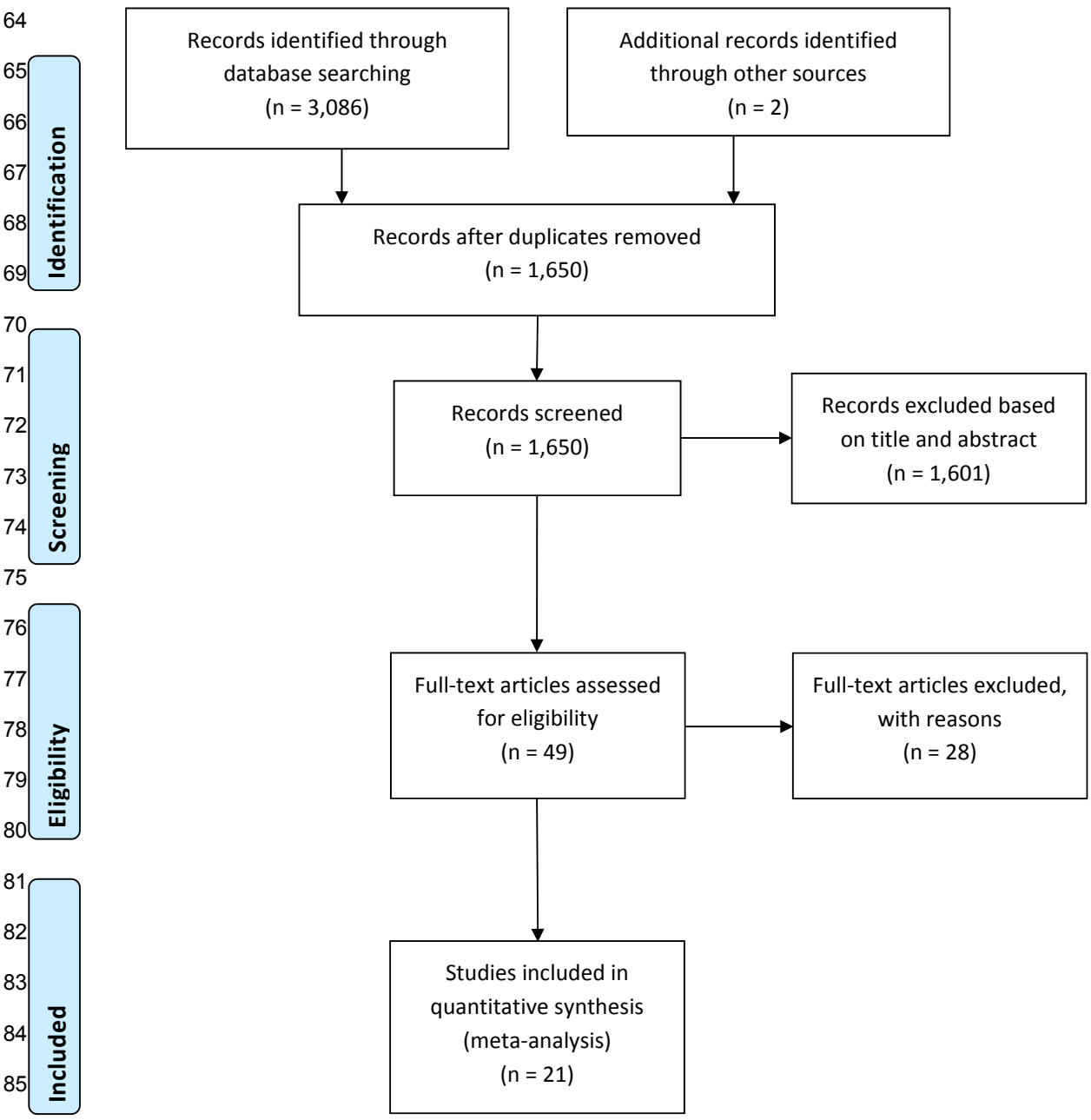
This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1: Literature Search

The literature search was performed on July 4, 2018 in the following data bases:
PubMed, Embase, Web of Science, COCHRANE Library, CENTRAL, Emcare, Academic Search Premier

We used the following search strategy:
(((subclinical hypothyroid*[ti] OR "subclinical hypothyroidism"[ti] OR "sub clinical hypothyroidism"[ti] OR (("sub-clinical"[ti] OR subclinical[ti] OR subclin*[ti] OR sub-clin*[ti]) AND ("Hypothyroidism"[majr:noexp] OR "hypothyroidism"[all fields] OR hypothyroid*[ti] OR hypo-thyroid*[ti]))) AND ("Thyroxine"[Mesh] OR "Thyroxine"[tw] OR thyroxin*[tw] OR levothyroxin*[tw] OR "T4 Thyroid Hormone"[tw] OR "O-(4-Hydroxy-3,5-diiodophenyl) 3,5-diiodo-L-tyrosine"[tw] OR "L-3,5,3',5'-Tetraiodothyronine"[tw] OR "Levothyroxine"[tw] OR "L-Thyroxine"[tw] OR "L Thyroxine"[tw] OR "3,5,3',5'-Tetraiodothyronine"[tw] OR "O-(4-Hydroxy-3,5-diiodophenyl)-3,5-diiodotyrosine"[tw] OR "L-Thyroxin Henning"[tw] OR "L Thyroxin Henning"[tw] OR "LThyroxin Henning"[tw] OR "Levothyroxine Sodium"[tw] OR "Sodium Levothyroxine"[tw] OR "Levoxine"[tw] OR "Levoxyl"[tw] OR "Lévothyrox"[tw] OR "L-Thyroxine Roche"[tw] OR "L Thyroxine Roche"[tw] OR "Levo-T"[tw] OR "Levo T"[tw] OR "LevoT"[tw] OR "Levothroid"[tw] OR "Novothyral"[tw] OR "Berlthyrox"[tw] OR "Dexnon"[tw] OR "Novothyrox"[tw] OR "Oroxine"[tw] OR "Synthroid"[tw] OR "Synthrox"[tw] OR "Thyrax"[tw] OR "Tiroidine"[tw] OR "Tiroxina Leo"[tw] OR "Unithroid"[tw] OR "Eferox"[tw] OR "Eltroxin"[tw] OR "Thevier"[tw] OR "Eltroxine"[tw] OR "Euthyrox"[tw] OR "Eutirox"[tw] OR "L-Thyrox"[tw] OR "L Thyrox"[tw] OR "L-Thyroxin beta"[tw] OR "L Thyroxin beta"[tw] OR "LThyroxin beta"[tw] OR "Levothyroid"[tw] OR "Levothyroxin Deladande"[tw] OR "Levothyroxin Delalande"[tw])) OR ((subclinical hypothyroid*[tw] OR "subclinical hypothyroidism"[tw] OR "sub clinical hypothyroidism"[tw] OR (("sub-clinical"[tw] OR subclinical[tw] OR subclin*[tw] OR sub-clin*[tw]) AND ("Hypothyroidism"[Mesh:noexp] OR "hypothyroidism"[all fields] OR hypothyroid*[tw] OR hypo-thyroid*[tw]))) AND ("Thyroxine"[majr] OR "Thyroxine"[ti] OR thyroxin*[ti] OR levothyroxin*[ti] OR "T4 Thyroid Hormone"[ti] OR "O-(4-Hydroxy-3,5-diiodophenyl) 3,5-diiodo-L-tyrosine"[ti] OR "L-3,5,3',5'-Tetraiodothyronine"[ti] OR "Levothyroxine"[ti] OR "L-Thyroxine"[ti] OR "L Thyroxine"[ti] OR "3,5,3',5'-Tetraiodothyronine"[ti] OR "O-(4-Hydroxy-3,5-diiodophenyl)-3,5-diiodotyrosine"[ti] OR "L-Thyroxin Henning"[ti] OR "L Thyroxin Henning"[ti] OR "LThyroxin Henning"[ti] OR "Levothyroxine Sodium"[ti] OR "Sodium Levothyroxine"[ti] OR "Levoxine"[ti] OR "Levoxyl"[ti] OR "Lévothyrox"[ti] OR "L-Thyroxine Roche"[ti] OR "L Thyroxine Roche"[ti] OR "Levo-T"[ti] OR "Levo T"[ti] OR "LevoT"[ti] OR "Levothroid"[ti] OR "Novothyral"[ti] OR "Berlthyrox"[ti] OR "Dexnon"[ti] OR "Novothyrox"[ti] OR "Oroxine"[ti] OR "Synthroid"[ti] OR "Synthrox"[ti] OR "Thyrax"[ti] OR "Tiroidine"[ti] OR "Tiroxina Leo"[ti] OR "Unithroid"[ti] OR "Eferox"[ti] OR "Eltroxin"[ti] OR "Thevier"[ti] OR "Eltroxine"[ti] OR "Euthyrox"[ti] OR "Eutirox"[ti] OR "L-Thyrox"[ti] OR "L Thyrox"[ti] OR "L-Thyroxin beta"[ti] OR "L Thyroxin beta"[ti] OR "LThyroxin beta"[ti] OR "Levothyroid"[ti] OR "Levothyroxin Deladande"[ti] OR "Levothyroxin Delalande"[ti]))) NOT ("Animals"[mesh] NOT "Humans"[mesh]) NOT (("Child"[mesh] OR "Infant"[mesh] OR "Adolescent"[mesh]) NOT "Adult"[mesh]) NOT ("Pregnancy"[majr] OR "Pregnancy Complications"[majr] OR pregnant*[ti] OR pregnanc*[ti])

eFigure: Flow Diagram of the Systematic Review (Study Selection)



93 **eTable 1:** Description of 28 Excluded Studies (After Independent Evaluation by Two Reviewers)

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Author, year	Study Design	n	Study population	Definition of thyroid dysfunction	Intervention	Outcome	Reason for exclusion
Chen,[1] 2018	RCT	92	SCH and diabetic nephropathy	TSH > 4.94 µIU/mL normal fT4, and T3	Levothyroxine	- Urinary albumin excretion rate - Lipids - Renal function	Patients with SCH & diabetic nephropathy Outcomes beyond scope of this review
Stott,[2] 2017	RCT	-	-	-	-	-	Publication of the protocol of the study by Stott et. al.[3]
Liu,[4] 2017	RCT	330	SCH	TSH >4.2mU/l + normal fT4 on 2 occasions	Levothyroxine	- Presence of non alcoholic fatty liver disease - Serum liver enzymes - Lipids - BMI - Glucose	Same study population and outcome (BMI) as in the included study by Zhao et. al.[5]
Razvi,[6] 2016	RCT	48	Patients with primary hypothyroidism under levothyroxine	Patients were euthyroid under levothyroxine	Levothyroxine	Feasability study	2 doses of levothyroxine were compared
Shahebrahimi,[7] 2015	RCT	100	SCH	TSH >4.7mU/l + normal fT4	Levothyroxine	Lipids	Outcomes beyond scope of this review
Liu,[8] 2015	RCT	136	SCH and diabetic nephropathy	TSH 4.0-7.0mU/l, normal fT4, TPO-Ab positive	Levothyroxine	- Urinary albumin excretion rate - Blood pressure - Lipids - Uric acid - Renal function	Patients with SCH & diabetic nephropathy
Deshmukh,[9] 2012	RCT	65	SCH	Adults with subclinical hypothyroidism	Levothyroxine	Quality of Life	No placebo control group, levothyroxine compared with “lifestyle measures”
Malek,[10] 2012	RCT	60	SCH	TSH >4.5mU/l, normal fT4, positive TPO-Ab	Levothyroxine	Cognitive function	Duplicate of the included study by Aghili et. al.[11]
Martins,[12] 2011	RCT	33	SCH	TSH >4mU/l + normal fT4 on 2 occasions	Levothyroxine	Echocardiographic measurments	Outcomes beyond scope of this review

Abu-Helalah,[13] 2010	RCT	56	SCH	Participants with family history of thyroid disease, with 'high' TSH, defined used a cut-off of 4.0 mU/L	Thyroxine	Quality of Life	Authors contacted, replied, but unable to provide necessary data
Teixeira,[14] 2008	RCT	-	-	-	-	-	Duplicate of the included study by Teixeira et. al.[15]
Mikhail,[16] 2008	RCT	120	SCH	TSH 4-10mU/l + normal fT4 on 2 occasions	Levothyroxine	Lipids	Outcomes beyond scope of this review
Kalantari,[17] 2006	RCT	80	SCH	TSH >5mU/l + normal fT4 on 2 occasions, TPO-Ab positive	Levothyroxine	Lipids	Outcomes beyond scope of this review
Franzoni,[18] 2006	RCT	42	SCH	TSH >3.6mU/l + normal fT3/4	Levothyroxine	Echocardiographic measurements	Outcomes beyond scope of this review
Fadeyev,[19] 2006	RCT	33	SCH + coronary artery disease	TSH >4mU/l (2 tests) + normal fT4	Levothyroxine	Lipids	- Outcomes beyond scope of this review - Study population with SCH & coronary artery disease
Christ-Crain,[20] 2005	Case-control and RCT	161	SCH	TSH >5mU/l on 2 consecutive tests, fT4 normal	Levothyroxine in the RCT subpopulation	Cardiac biomarkers	Outcomes beyond scope of this review
Meier,[21] 2004	RCT	66	Same study population as in Christ-Crain et. al.(2003)	TSH >5mU/l on 2 consecutive tests, fT4 normal	Levothyroxine	Bone turnover markers	Outcomes beyond scope of this review
Christ-Crain,[22] 2004	RCT	66	Same study population as in Christ-Crain et. al.(2003)	TSH >5mU/l on 2 consecutive tests, fT4 normal	Levothyroxine	Surrogate markers of skeletal and cardiac function	Outcomes beyond scope of this review
Meier,[23] 2003	RCT	66	Same study population as in Christ-Crain et. al.(2003)	TSH >5mU/l on 2 consecutive tests, fT4 normal	Levothyroxine	Prolactin	Outcomes beyond scope of this review
Christ-Crain,[24] 2003	RCT	66	SCH	TSH >5mU/l on 2 consecutive tests, fT4 normal	Levothyroxine	Hematologic parameters	Outcomes beyond scope of this review
Kong,[25] 2002	RCT	-	-	-	-	-	Duplicate of the included study by Kong et. al.[26]

Jensovsky,[27] 2002	Interventional	60	SCH + controls	Not explicitly reported	Levothyroxine	Electroencephalo-graphy	Not randomized
Biondi,[28] 1999	Interventional	56	SCH + Control	Elevated TSH + fT4 “low normal”	Thyroxine	Echocardiographic measurements	Not randomized
Jaeschke,[29] 1996	RCT	31	SCH	TSH >6mU/l on ≥2 occasions + normal fT3/4	Levothyroxine	- Quality of Life, - Fatigue, - Mood, - Cognition	Authors contacted, replied, but unable to provide necessary data
Ross,[30] 1993	RCT	17	SCH	Elevated TSH + normal fT4	Levothyroxine	Bone mineral density	Outcomes beyond scope of this review
Nikolai,[31] 1990	Interventional	22	Women with premenstrual syndrome	-	-	-	Study population does not have SCH
Nyström,[32] 1988	RCT	20	Women with SCH	Patients with baseline TSH above 4.0mU /l without clinical evidence of thyroid disease, having T4,free T4 and T3 concentrations within the reference interval but exaggerated TSH response (TSH above 30 mU/l) upon thyroliberin administration	Levothyroxine	- Quality of Life - Cognition	Authors contacted, but no reply received (corresponding author retired)
Evered,[33] 1973	Interventional	22	Hypothyroidism	Elevated TSH + hypothyroid symptoms	Thyroxine	Normal TSH concentration	No control group

Abbreviations: **y**, year; **RCT**, randomized controlled trial; **n**, number of participants; **SCH**, subclinical hypothyroidism; **TSH**, thyroid-stimulating hormone; **fT4**, free thyroxine; **TPO-Ab**, thyroid peroxidase antibody.

eTable 2: Detailed Results of 21 Included RCTs on thyroid Hormone Replacement Therapy in Non-pregnant Adults With Subclinical Hypothyroidism, Stratified by Outcomes

Study, year Study duration	Intervention vs. placebo - N - Mean TSH, - at baseline - at follow-up	Outcome Original results (Intervention vs placebo) B: baseline E: at end of intervention	SMD (95%CI)[a]
Thyroid-related symptoms / General quality of life / Tiredness/Fatigue / Depressive Symptoms			
Stott,[3] 2017 12 months	368 vs 369 6.4 vs 6.4 3.6 vs 5.5	**ThyPRO Hypothyroid symptoms score** B: 17.5 (±18.8) vs 16.9 (±17.9) E: 16.6 (±16.9) vs 16.7 (±17.5) Difference (95%CI) 0.0 (-2.0 to 2.1)	0.01 (-0.15 to 0.16)
		Quality of life (EQ-5D) B: 0.85 (±0.19) vs 0.85 (±0.17) E: 0.83 (±0.21) vs 0.85 (±0.19) Difference (95%CI) -0.03 (-0.05 to 0.00)	-0.10 (-0.25 to 0.06)
		ThyPRO Tiredness score B: 25.9 (±20.6) vs 25.5 (±20.3) E: 28.7 (±20.2) vs 28.6 (±19.5) Difference (95%CI) 0.4 (-2.1 to 2.9)	-0.01 (-0.16 to 0.15)
Najafi,[34] 2015 3 months	30 vs 30 8.3 vs 8.1 2.0 vs 7.8	**Depressive symptoms (BDI)** B: 16.8 (±13.3) vs 13.8 (±11.7) E: 12.4 (±10.0) vs 11.9 (±10.7)	-0.05 (-0.56 to 0.46)
Reuters,[35] 2012 6 months	35 vs 36 7.3 vs 7.6 nr vs nr	**Hypothyroid symptoms (Zulewski score)** Post-treatment / pre-treatment difference (SD) Levothyroxine: -0.5 (±1.2) Placebo: -0.8 (±1.6)	-0.22 (-0.74 to 0.31)
		Quality of life (SF-36) Post-treatment / pre-treatment difference (SD) Levothyroxine: 9.9 (±27.0) Placebo: 0.7 (±26.1)	0.35 (-0.18 to 0.87)
		Depressive symptoms (BDI) Post-treatment / pre-treatment difference (SD) Levothyroxine: -2.4 (±5.8) Placebo: -2.1 (±4.8)	0.06 (-0.56 to 0.46)
Parle,[36] 2010 12 months	52 vs 42 6.6 vs 6.6 3.7 vs 5.5	**Depressive symptoms (HADS)** B: 3.4 (±2.6) vs 2.9 (±2.6) E: 3.6 (±2.5) vs 3.3 (±2.8) Difference (95%CI) 0.18 (-0.64 to 1.00)	-0.11 (-0.52 to 0.29)
Razvi,[37] 2007 3 months	100 (cross-over) 5.3 0.5	**(Thyroid-related) Quality of life (ThyDQoL)** Effect under L-thyroxine -1.1 (±1.0) Effect under placebo -1.2 (±0.9) Difference (95%CI) 0.2 (0.02 to 0.36)	0.11 (-0.29 to 0.50)
Jorde,[38] 2006 12 months	36 vs 33 5.8 vs 5.3 1.5 vs 5.4	**Quality of life (GHQ-30 (total score))** B: 1.5 (±2.3) vs 0.7 (±1.3) E: 1.9 (±3.3) vs 1.2 (±2.0)	-0.25 (-0.74 to 0.23)
		Depressive symptoms (BDI) B: 4.4 (±3.7) vs 3.7 (±3.8) E: 4.3 (±3.6) vs 3.3 (±3.3)	-0.26 (-0.74 to 0.22)

Kong,[26] 2002 6 months	23 vs 17 8.0 vs 7.3 3.4 vs 5.6	**Quality of life (GHQ-30)** B (IQR): 5 (0 to 15) vs 5 (2 to 11) Change from baseline to 6 months (IQR) -3 (-11 to 1) vs -5 (-10 to -1)	-1.00 (-1.73 to -0.27)
Meier,[39] 2001 12 months	33 vs 33 12.8 vs 10.7 3.1 vs 9.9	**Hypothyroid symptoms (Billewicz score)** B: -25.7 (±15.2) vs -28.3 (±14.1) E: -32.1 (±11.9) vs -30.8 (±14.1)	0.10 (-0.39 to 0.59)
Cognitive function			
Stott,[3] 2017 18 months	368 vs 369 6.4 vs 6.4 3.6 vs 5.5	**Letter-digit coding test** B: 28.0 (±10.2) vs 25.2 (±8.3) E: 27.5 (±10.5) vs 27.1 (±11.2) Between group difference (95%CI) at final follow-up visit -0.1 (-0.9, 0.7)	0.04 (-0.12 to 0.19)
Aghili,[11] 2012 3 months	30 vs 30 8.3 vs 8.1 2.0 vs 7.8	**Wechsler memory scale** B: 105.7 (±11.7) vs 105.9 (±11.5) E: 115.6 (±14.0) vs 109.1 (±13.7) Change from baseline to 3 months 9.9 (±8.0) vs 3.2 (±7.6)	0.47 (-0.04 to 0.98)
Parle,[36] 2010 12 months	52 vs 42 6.6 vs 6.6 3.7 vs 5.5	**MMSE** 28.3 (±2.0) vs 28.2 (±2.1) 28.3 (±2.1) vs 28.3 (±1.9) Difference (95%CI) 0.03 (-1.12 to 1.17)	0.01 (-0.39 to 0.42)
Jorde,[38] 2006 12 months	36 vs 33 5.8 vs 5.3 1.5 vs 5.4	**Composite cognitive score (range unclear, higher scores mean better cognition)** B: 1.8 (±3.4) vs -1.1 (±4.7) E: 1.5 (±3.7) vs -0.9 (±4.8)	0.32 (-0.17 to 0.80)
Muscle strength			
Stott,[3] 2017 12 months	368 vs 369 6.4 vs 6.4 3.6 vs 5.5	**Handgrip strength (in kg)** B: 28.0 (±10.2) vs 27.5 (±11.3) E: 27.5 (±10.5) vs 27.1 (±11.2) Difference (95%CI) -0.1 (-0.9 to 0.7)	0.0 (-0.1 to 0.2)
Reuters,[35] 2012 6 months	35 vs 36 7.3 vs 7.6 nr vs nr	**Isometric quadriceps strengths (in % of age-, sex-, weight- and height-adjusted reference values)** Post-treatment / pre-treatment difference (SD) Levothyroxine: 5.3 (±11.2) Placebo: 0.8 (±19.6)	0.3 (-0.2 to 0.8)
Blood pressure			
Stott,[3] 2017 12 months	368 vs 369 6.4 vs 6.4 3.6 vs 5.5	**Systolic** B: 141.2 (±18.7) vs 140.4 (±18.9) E: 138.3 (±18.7) vs 138.4 (±17.8)	na
		Diastolic B: 74.1 (±11.6) vs 74.8 (±11.7) E: 72.8 (±11.4) vs 73.5 (±11.1)	na
Zhao,[5] 2016 15 months	210 vs 159 6.0 vs 5.5 2.8 vs 4.9	**Systolic** B: 148.6 (±20.0) vs 150.7 (±23.8) E: 136.1 (±20.1) vs 138.6 (±19.8)	na
		Diastolic B: 84.5 (±11.4) vs 85.8 (±11.5) E: 79.4 (±11.0) vs 79.6 (±11.2)	na

Ersoy,[40] 2012 6 months	30 vs 30 7.5 vs 6.8 3.6 vs 7.8	**Systolic** B: 132.5 (±19.0) vs 127.8 (±18.8) E: 131.7 (±17.9) vs 129.2 (±17.9)	na
		Diastolic B: 79.8 (±10.4) vs 73.7 (±12.0) E: 79.0 (±10.3) vs 74.3 (±11.5)	na
Nagasaki,[41] 2009 5 months	48 vs 47 7.3 vs 7.3 2.7 vs 7.0	**Systolic** B: 132.8 (±26.7) vs 133.1 (23.1) E: 128.8 (±26.1) vs 132.2 (±26.1)	na
		Diastolic B: 74.3 (±19.7) vs 75.7 (±13) E: 72.7 (±15.1) vs 72.8 (±13.6)	na
Razvi,[37] 2007 3 months	100 (cross-over) 5.3 0.5	**Systolic** E: 132.8 (±22.8) vs 134.6 (±22.9) Difference (95%CI) -1.8 (-4.6 to 1.0)	na
		Diastolic E: 78.8 (±10.3) vs 79.9 (±9.6) Difference (95%CI) -1.1 (-2.8 to 0.5)	na
Yazici,[42] 2004 12 months	23 vs 22 8.5 vs 8.4 2.4 vs 8.4	**Systolic** B: 124.1 (±11.9) vs 122.9 (±12.1) E: 123.6 (±9.8) vs 123.1 (±9.8)	na
		Diastolic B: 77.9 (±9.8) vs 78.5 (±7.9) E: 76.7 (±8.9) vs 77.2 (±8.3)	na
Monzani,[43] 2004 6 months	23 vs 22 6.0 vs 5.7 1.3 vs 6.0	**Systolic** B: 117 (±15) vs 112 (±13) E: 112 (±15) vs 114 (±13)	na
		Diastolic B: 72 (±11) vs 71 (±9) E: 69.9 (±9) vs 72 (±8)	na
Monzani,[44] 2001 6 months	10 vs 10 5.4 vs 4.7 1.3 vs 4.6	**Systolic** B: 115.3 (±7.1) vs 116.7 (±9.5) E: 117.3 (±6.8) vs 116.8 (±9.6)	na
		Diastolic B: 75.3 (±4.2) vs 70.5 (±6.9) E: 74.8 (±7.2) vs 71.0 (±7.0)	na
Body-mass index			
Stott,[3] 2017 12 months	368 vs 369 6.4 vs 6.4 3.6 vs 5.5	B: 28.1 (±5.3) vs 27.7 (±4.6) E: 27.9 (±5.1) vs 27.7 (±4.6)	na
Zhao,[5] 2016 15 months	210 vs 159 6.0 vs 5.5 2.8 vs 4.9	B: 26.0 (±3.2) vs 25.7 (±3.6) E: 25.8 (±3.2) vs 25.7 (±3.6)	na
Ersoy,[40] 2012 6 months	30 vs 30 7.5 vs 6.8 3.6 vs 7.8	B: 30.1 (±6.1) vs 28.7 (±4.3) E: 30.1 (±6.0) vs 28.9 (±4.2)	na
Cabral,[45] 2011 12 months[b]	14 vs 18 6.8 vs 6.8 3.0 vs 6.7	B: 25.9 (±2.3) vs 26.2 (±2.7) E: 25.8 (±2.3) vs 25.7 (±3.0)	na
Nagasaki,[41] 2009 5 months	48 vs 47 7.3 vs 7.3 2.7 vs 7.0	B: 22.0 (±3.2) vs 22.2 (±3.5) E: 21.8 (±3.2) vs 22.1 (±3.4)	na
Teixeira,[15] 2008 12 months	35 vs 25 7.5 vs 7.7 2.1 vs 4.9	B: 26.7 (±1.7) vs 24.1 (±3.2) E: 27.4 (±3.2) vs 24.5 (±3.3)	na
Razvi,[37] 2007 3 months[b,c]	50 vs 50 5.4 vs 5.3 nr vs nr	B: 28.2 (±5.0) vs 28.8 (±5.4) E: 28.1 (±5.2) vs 28.4 (±5.3)	na

Iqbal,[46] 2006 12 months	32 vs 32 5.8 vs 5.4 1.5 vs 5.4	B: 28.7 (±5.7) vs 27.1 (±3.7) E: 28.4 (±5.8) vs 27.0 (±4.1)	na
Caraccio,[47] 2005 6 months	12 vs 11 4.4 vs 5.0 1.3 vs 5.1	B: 22.8 (±3.0) vs 22.6 (±1.9) E: 22.3 (±3.0) vs 22.7 (±1.9)	na
Yazici,[42] 2004 12 months	23 vs 22 8.5 vs 8.4 2.4 vs 8.4	B: 23.4 (±2.6) vs 22.9 (±2.8) E: 22.8 (±3.4) vs 23.0 (±3.1)	na
Monzani,[43] 2004 6 months	23 vs 22 6.0 vs 5.7 1.3 vs 6.0	B: 24.3 (±3.6) vs 25.0 (±3.5) E: 23.7 (±3.5) vs 24.9 (±3.8)	na
Kong,[26] 2002 6 months	23 vs 17 8.0 vs 7.3 3.4 vs 5.6	B: 25.5 (±3.2) vs 27.2 (±4.9) E: 25.4 (±3.2) vs 27.4 (±4.9)	na
Caraccio,[48] 2002 6 months	24 vs 25 6.0 vs 4.9 1.5 vs 4.9	B: 24.2 (±3.2) vs 22.5 (±2.5) E: 24.1 (±3.1) vs 22.8 (±2.7)	na
Monzani,[44] 2001 6 months	10 vs 10 5.4 vs 4.7 1.3 vs 4.6	B: 23.5 (±4.8) vs 23.0 (±2.3) E: 23.1 (±4.7) vs 23.1 (±2.2)	na
Cooper,[49] 1984 12 months	17 vs 16 10.8 vs 11.1 2.6 vs 14.7	B: 28.0 (±2.6) vs 25.0 (±4.6) E: 28.1 (±2.6) vs 24.6 (±4.9)	na
Cardiovascular events / Mortality / Side effects (hyperthyroidism due to overdosing)			
Stott,[3] 2017 12 months	368 vs 369 6.4 vs 6.4 3.6 vs 5.5	**Fatal or nonfatal** 18 (4.9%) vs 20 (5.4%) Hazard ratio 0.89 (0.47 to 1.69)	na
		Mortality 10 (2.7%) vs 5 (1.4%) Hazard ratio 1.91 (0.65 to 5.60)	na
		Hyperthyroidism symptom score B: 10.5 (±11.2) vs 10.5 (±11.2) E: 10.5 (±10.8) vs 10.3 (±11.3) Difference (95%CI) 0.6 (-0.7 to 1.9)	na

Abbreviations: **(± x)** indicate Standard deviations, if not stated otherwise; **N**, number of participants; **SMD**, standardized mean difference; **CI**, confidence interval; **SE**, Standard error; **TSH**, thyroid-stimulating hormone (mIU/liter); **nr**, not reported; **EQ-5D**, Euro quality of life 5 dimensions questionnaire (range -0.59 to 1.00, higher scores indicate better quality of life); **ThyPRO** (Thyroid-related quality-of-life patient-reported outcome) **Hypothyroid Symptoms Score** (range 0 to 100, higher scores indicate more hypothyroid symptoms); **ThyPRO Tiredness score** (range 0 to 100, higher scores indicate more tiredness); **BDI**, Becks depression inventory (range 0 to 63, higher scores indicate worse depressive symptoms); **Zulewski score** (range 0 to 12 points, higher scores indicate worse hypothyroid symptoms); **SF-36**, Short Form Health Survey (range 0 to 100, higher scores indicate better quality of life); **HADS**, Hospital anxiety and depression scale (range 0 to 21, higher scores indicate worse depressive symptoms); **ThyDQoL**, 18-item underactive thyroid-dependent quality of life (range -9 to 3, higher scores indicate better quality of life); **QHC-30**, General health questionnaire 30 items (range 0 to 90 with Likert scoring, otherwise range 0 to 30, higher scores indicate worse quality of life); **IQR**, Interquartile range; **Billewicz score** (range -47 to 67, higher scores indicates worse hypothyroid symptoms); **Letter-digit coding test** (minimum score is 0, with higher scores indicating better executive cognitive function; there is no maximum score); **Wechsler memory scale** (range 40 to 160, higher scores indicate better cognitive function); **MMSE**, Mini-Mental State Examination (range 0 to 30, higher scores indicate better cognition); **Hyperthyroidism symptom score** (range 0 to 100, higher scores indicate more hyperthyroid symptoms); **na**, not applicable.

[a] Positive values indicate benefit of thyroid hormone replacement therapy

[b] Data obtained through direct communication with author

[c] This is actually a cross-over trial. However, for body-mass index, we only analyzed the first three months of treatment (before cross-over), i.e. the 50 participants initially randomized to levothyroxine vs the 50 participants initially randomized to placebo

eTable 3: Risk of Bias Assessment of the 21 Included Randomized Controlled Trials, Adapted From a Template Suggested by the Cochrane Collaboration[50] (See at the End of this Appendix, Section 5)

Author, year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Stott,[2] 2017	Low	Low	Low	Low	Low	Low
Zhao,[5] 2016	Low	Low	High	High	Low	High
Najafi,[34] 2015[a]	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Ersoy,[40] 2012	Low	Unclear	High	High	Unclear	Unclear
Aghili,[11] 2012[a]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Reuters,[35] 2012	Unclear	Low	Low	Low	High	Unclear
Cabral,[45] 2011	Low	Low	High	Low	Low	Unclear
Parle,[36] 2010	Low	Low	Low	Low	Unclear	Unclear
Nagasaki,[41] 2009	Unclear	Unclear	Low	Low	Low	Unclear
Teixeira,[15] 2008	Unclear	Unclear	Low	Low	High	Unclear
Razvi,[37] 2007	Unclear	Unclear	Low	Low	Low	Low
Jorde,[38] 2006[b]	Unclear	Unclear	Unclear	Low	Low	Unclear
Iqbal,[46] 2006[b]	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Caraccio,[47] 2005	Unclear	Low	Low	Low	Low	Unclear
Yazici,[42] 2004	Unclear	Low	Low	Low	Low	Unclear
Monzani,[43] 2004	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Kong,[26] 2002	Low	Low	Low	Low	High	Unclear
Caraccio,[48] 2002	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Monzani,[44] 2001	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Meier,[39] 2001	Low	Low	Low	Low	Low	Low
Cooper,[49] 1984	Unclear	Unclear	Unclear	Low	Low	Unclear

[a, b] These two studies used identical study populations, but reported different outcomes

eTable 4: Summary of Findings and Quality of Evidence (GRADE) on the Effect of Thyroid Hormone Therapy in Non-pregnant Adults With Subclinical Hypothyroidism

Outcomes	Pooled effect[a] (95% CI) I^2, p-value	Number of participants (studies)	Quality of evidence (GRADE)[b]	Comments
General quality of life Follow-up [range]: 6 – 12 months	-0.11 (-0.25 to 0.03) 66.7%, p=0.029	796 (4 RCTs)	☒ ☒ ☒ ☒ High[c]	- Positive values indicate benefit of thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☐ (downgrade 1) - Indirectness ☒ - Imprecision ☒ - Publication bias ☒
Thyroid-related symptoms Follow-up [range]: 3 – 12 months	0.01 (-0.12 to 0.14) 0.0%, p=0.79	858 (4 RCTs)	☒ ☒ ☒ ☒ High	- Positive values indicate benefit of thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☒ - Indirectness ☒ - Imprecision ☒ - Publication bias ☒
Depressive symptoms Follow-up [range]: 6 – 12 months	-0.10 (-0.34 to 0.13) 0.0%, p=0.84	278 (4 RCTs)	☒ ☒ ☒ ☐ Moderate	- Positive values indicate benefit of thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☒ - Indirectness ☒ - Imprecision ☐ (downgrade 1) - Publication bias ☒
Fatigue / tiredness Follow-up: 12 months	-0.01 (-0.16 to 0.15) na	638 (1 RCT)	☒ ☒ ☒ ☐ Moderate[d]	- Positive values indicate benefit of thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☐ na - Indirectness ☒ - Imprecision ☒ - Publication bias ☒

Cognitive function Follow-up [range]: 3 – 18 months	0.09 (-0.05 to 0.22) 14.7%, p=0.32	859 (4 RCTs)	☒ ☒ ☒ ☐ Moderate	- Positive values indicate benefit of thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☒ - Indirectness ☒ - Imprecision ☐ (downgrade 1) - Publication bias ☒
Muscle strength Follow-up [range]: 6 - 12 months	0.1 (-0.1 to 0.2) 0.0%, p=0.36	695 (2 RCT)	☒ ☒ ☒ ☒ Moderate	- Positive values indicate benefit of thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☒ - Indirectness ☒ - Imprecision ☒ - Publication bias ☒
Blood pressure (systolic, in mmHg) Follow-up [range]: 3 – 12 months	-0.7 (-2.6 to 1.2) 0.0%, p=0.95	1,372 (8 RCTs)	☒ ☒ ☒ ☒ High	- Negative values indicate benefit of thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☒ - Indirectness ☒ - Imprecision ☒ - Publication bias ☒
Blood pressure (diastolic, in mmHg) Follow-up [range]: 3 – 12 months	-0.3 (-1.4 to 0.6) 0.0%, p=0.50	1,372 (8 RCTs)	☒ ☒ ☒ ☒ High	- Negative values indicate benefit of thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☒ - Indirectness ☒ - Imprecision ☒ - Publication bias ☒
Body-mass index (in kg/m^2) Follow-up [range]: 3 – 12 months	0.2 (-0.4 to 0.8) 45.5%, p=0.028	1,633 (15 RCTs)	☒ ☒ ☒ ☒ High[e]	- Negative values indicate benefit of thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☐ (downgrade 1) - Indirectness ☒ - Imprecision ☒ - Publication bias ☒

Cardiovascular events Follow-up: 12 months	Hazard ratio 0.89 (0.47 to 1.69)	737 (1 RCT)	☒ ☒ ☐ ☐ Low[f]	- Values <1 indicate benefit of thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☐ na - Indirectness ☒ - Imprecision ☐ (downgrade 2) - Publication bias ☒
Mortality Follow-up: 12 months	Hazard ratio 1.91 (0.65 to 5.60)	737 (1 RCT)	☒ ☒ ☐ ☐ Low[f]	- Values <1 indicate benefit of thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☐ na - Indirectness ☒ - Imprecision ☐ (downgrade 2) - Publication bias ☒
Side effects (hyperthyroidism due to overdosing) Follow-up: 12 months	Difference in symptom score 0.6 (-0.7 to 1.9)	638 (1 RCT)	☒ ☒ ☒ ☐ Moderate[d]	- Positive values indicate more side effects due to thyroid hormone therapy - Risk of bias assessment ☒ - Inconsistency ☐ na - Indirectness ☒ - Imprecision ☒ - Publication bias ☒

Abbreviations: **CI**, confidence interval; **na**, not applicable;

[a] Standardized mean difference (if not stated otherwise) from random effect meta-analysis, positive values indicate benefit of thyroid hormone therapy

[b] **GRADE** working group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[c] Upgrade of 1 as inconsistency was driven by one study showing benefit of placebo. Thus, we consider it high quality evidence that thyroid hormone therapy does not confer benefit.

[d] As only 1 well-conducted, adequately sized RCT is available for this outcome, we decided to downgrade 1

[e] Upgrade of 1 as we consider it high quality evidence that thyroid hormone therapy does not confer benefit (downgrade was due to inconsistency, but the "outlier" studies were in the direction of lower body-mass index under placebo).

[f] Downgrade 2 due to imprecision (results compatible with benefit as well as harm due to thyroid hormone therapy). Only one RCT reported on cardiovascular events and mortality, and the mean follow-up was 17 months, too short to thoroughly examine these outcomes.

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eAppendix 2:

Data collection form (adapted)

Intervention review – RCTs

This form can be used as a guide for developing your own data extraction form. Sections can be expanded and added, and irrelevant sections can be removed. It is difficult to design a single form that meets the needs of all reviews, so it is important to consider carefully the information you need to collect, and design your form accordingly. Information included on this form should be comprehensive, and may be used in the text of your review, 'Characteristics of included studies' table, risk of bias assessment, and statistical analysis.

Notes on using a data extraction form:

- Be consistent in the order and style you use to describe the information for each included study.
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.
- Include any instructions and decision rules on the data collection form, or in an accompanying document. It is important to practice using the form and give training to any other authors using the form.
- You will need to protect the document in order to use the form fields (Tools / Protect document)

Review title or ID
Thyroid hormone replacement therapy for subclinical hypothyroidism: a systematic review and meta-analysis of randomized-controlled trials

Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*

Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*

Notes:

1. General Information

1. **Date form completed** *(dd/mm/yyyy)*	
2. **Name/ID of person extracting data**	
3. **Report title** *(title of paper/ abstract/ report that data are extracted from)*	

4. **Report ID** *(if there are multiple reports of this study)*	
5. **Reference details**	
6. **Report author contact details**	
7. **Publication type** *(e.g. full report, abstract, letter)*	
8. **Study funding source** *(including role of funders)*	
Possible conflicts of interest *(for study authors)*	
9. **Notes:** Protocol registration number:	

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Study Characteristics	**Review Inclusion Criteria** *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	**Yes/ No / Unclear**	**Location in text** *(pg & ¶/fig/table)*
10. **Type of study**	Randomised trial	...	
	Non-randomised trial	...	
	Controlled before-after study • Contemporaneous data collection • At least 2 intervention and 2 control clusters	...	
	Interrupted time series OR Repeated measures study • At least 3 timepoints before and 3 after the intervention • Clearly defined intervention point	... ...	
	Other design (specify):	...	
11. **Participants**		...	
12. **Types of intervention**		...	
13. **Types of outcome measures**		...	
14. **Decision:**	...		
15. **Reason for exclusion**			
16. **Notes:**			

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318 **DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW**
319

3. Population and setting

	Description *Include comparative information for each group (i.e. intervention and controls) if available*	**Location in text** *(pg & ¶/fig/table)*
17. **Population description** *(from which study participants are drawn)*		
18. **Setting** *(including location and social context)*		
19. **Inclusion criteria**		
20. **Exclusion criteria**		
21. **Method/s of recruitment of participants**		
22. **Notes:**		

4. Methods

	Descriptions as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
23. **Aim of study**		
24. **Design** *(has to be RCT)*		
25. **Unit of allocation** *(by individuals, cluster/ groups or body parts)*		
26. **Start date**		
27. **End date**		
28. **Duration of participation** *(from recruitment to last follow-up)*		
29. **Notes:**		

5. Risk of Bias assessment

See Chapter 8 of the Cochrane Handbook. Additional domains may be required for non-randomised studies.

Domain	**Risk of bias** *Low/ High/Unclear*	**Support for judgement**	**Location in text** *(pg & ¶/fig/table)*
30. **Random sequence generation** *(selection bias)*	…		
31. **Allocation concealment** *(selection bias)*	…		
32. **Blinding of participants and personnel** *(performance bias)*	…	**Outcome group: All/**	
(if required)	…	**Outcome group:**	
33. **Blinding of outcome assessment** *(detection bias)*	…	**Outcome group: All/**	
(if required)	…	**Outcome group:**	
34. **Incomplete outcome data** *(attrition bias)*	…		
35. **Selective outcome reporting?** *(reporting bias)*	…		
36. **Other bias**	…		
37. **Notes:**			

6. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	**Location in text** (pg & ¶/fig/table)
38. **Total no. randomised** *(or total pop. at start of study for NRCTs)*		
39. **Clusters** *(if applicable, no., type, no. people per cluster)*		
40. **Baseline imbalances**		

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
41. **Withdrawals and exclusions** *(if not provided below by outcome)*		
42. **Age**		
43. **Sex**		
44. **Race/Ethnicity**		
45. **Severity of illness**		
46. **Co-morbidities**		
47. **Other treatment received** *(additional to study intervention)*		
48. **Other relevant sociodemographics**		
49. **Subgroups measured**		
50. **Subgroups reported**		
51. **Notes:**		

7. Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
52. **Group name**		
53. **No. randomised to group** *(specify whether no. people or clusters)*		
54. **Description** *(include sufficient detail for replication, e.g. content, dose, components; if it is a natural experiment, describe the pre-intervention)*		
55. **Duration of treatment period**		
56. **Timing** *(e.g. frequency, duration of each episode)*		

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
57. **Delivery** *(e.g. mechanism, medium, intensity, fidelity)*		
58. **Providers** *(e.g. no., profession, training, ethnicity etc. if relevant)*		
59. **Co-interventions**		
60. **Economic variables** *(i.e. intervention cost, changes in other costs as result of intervention)*		
61. **Resource requirements to replicate intervention** *(e.g. staff numbers, cold chain, equipment)*		
62. **Notes:**		

Control Group

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
63. **Group name**		
64. **No. randomised to group** *(specify whether no. people or clusters)*		
65. **Description** *(include sufficient detail for replication, e.g. content, dose, components; if it is a natural experiment, describe the pre-intervention)*		
66. **Duration of treatment period**		
67. **Timing** *(e.g. frequency, duration of each episode)*		
68. **Delivery** *(e.g. mechanism, medium, intensity, fidelity)*		

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
69. **Providers** *(e.g. no., profession, training, ethnicity etc. if relevant)*		
70. **Co-interventions**		
71. **Economic variables** *(i.e. intervention cost, changes in other costs as result of intervention)*		
72. **Resource requirements to replicate intervention** *(e.g. staff numbers, cold chain, equipment)*		
73. **Notes:**		

8. Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	Location in text *(pg & ¶/fig/table)*
74. **Outcome name**		
75. **Time points measured** *(specify whether from start or end of intervention)*		
76. **Time points reported**		
77. **Outcome definition** *(with diagnostic criteria if relevant and note whether the outcome is desirable or undesirable if this is not obvious)*		
78. **Person measuring/ reporting**		
79. **Unit of measurement** *(if relevant)*		

	Description as stated in report/paper		Location in text *(pg & ¶/fig/table)*
80. **Scales: upper and lower limits** *(indicate whether high or low score is good)*			
81. **Is outcome/tool validated?**	... *Yes/No/Unclear*		
82. **Imputation of missing data** *(e.g. assumptions made for ITT analysis)*			
83. **Assumed risk estimate** *(e.g. baseline or population risk noted in Background)*			
84. **Notes:**			

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

For randomised or non-randomised trial - Dichotomous outcome

	Description as stated in report/paper				Location in text *(pg & ¶/fig/table)*
85. **Comparison**					
86. **Outcome**					
87. **Subgroup**					
88. **Time point** *(specify whether from start or end of intervention)*					
89. **Results** *Note whether:* **...** *post-intervention OR* **...** *change from baseline And whether* **...** *Adjusted OR* **...***Unadjusted*	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	
90. **Baseline data**	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	

	Description as stated in report/paper		Location in text *(pg & ¶/fig/table)*
91. **No. missing participants and reasons**			
92. **No. participants moved from other group and reasons**			
93. **Any other results reported**			
94. **Unit of analysis** *(e.g. by individuals, health professional, practice, hospital, community)*			
95. **Statistical methods used and appropriateness of these methods** *(e.g. adjustment for correlation)*			
96. **Reanalysis required?** *(if yes, specify why, e.g. correlation adjustment)*	… *Yes/No/Unclear*		
97. **Reanalysis possible?**	… *Yes/No/Unclear*		
98. **Reanalysed results**			
99. **Notes:**			

343 **For randomised or non-randomised trial - Continuous outcome**

	Description as stated in report/paper						Location in text *(pg & ¶/fig/table)*
100. **Comparison**							
101. **Outcome**							
102. **Subgroup**							
103. **Time point** *(specify whether from start or end of intervention)*							
104. **Post-intervention or change from baseline?**							
105. **Results** *Note whether:* **…** *post-intervention OR*	**Intervention**			**Comparison**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	

	Description as stated in report/paper						Location in text *(pg & ¶/fig/table)*
... *change from baseline And whether* **...** *Adjusted OR* **...***Unadjusted*							
106. **Baseline data**	**Intervention**			**Comparison**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
107. **No. missing participants and reasons**							
108. **No. participants moved from other group and reasons**							
109. **Any other results reported**							
110. **Unit of analysis** *(e.g. by individuals, health professional, practice, hospital, community)*							
111. **Statistical methods used and appropriateness of these methods** *(e.g. adjustment for correlation)*							
112. **Reanalysis required?** *(if yes, specify why)*	... *Yes/No/Unclear*						
113. **Reanalysis possible?**	... *Yes/No/Unclear*						
114. **Reanalysed results**							
115. **Notes:**							

344 **For randomised or non-randomised trial - Other outcome**

	Description as stated in report/paper				Location in text *(pg & ¶/fig/table)*
116. **Comparison**					
117. **Outcome**					
118. **Subgroup**					
119. **Time point** *(specify whether from start or end of intervention)*					
120. **Type of outcome**					
121. **Results**	Intervention result	SD (or other variance)	Control result	SD (or other variance)	
	Overall results		SE (or other variance)		
122. **No. participant**	Intervention		Control		
123. **No. missing participants and reasons**					
124. **No. participants moved from other group and reasons**					
125. **Any other results reported**					
126. **Unit of analysis** *(e.g. by individuals, health professional, practice, hospital, community)*					
127. **Statistical methods used and appropriateness of these methods**					
128. **Reanalysis required?** *(if yes, specify why)*	...				
129. **Reanalysis possible?**	...				
130. **Reanalysed results**					
131. **Notes:**					

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10. Applicability

132. **Have important populations been excluded from the study?** *(consider disadvantaged populations, and possible differences in the intervention effect)*	... *Yes/No/Unclear*	
133. **Is the intervention likely to be aimed at disadvantaged groups?** *(e.g. lower socioeconomic groups)*	... *Yes/No/Unclear*	
134. **Does the study directly address the review question?** *(any issues of partial or indirect applicability)*	... *Yes/No/Unclear*	
135. **Notes:**		

11. Other information

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
136. **Key conclusions of study authors**		
137. **References to other relevant studies**		
138. **Correspondence required for further study information** *(what and from whom)*		
139. **Further study information requested** *(from whom, what and when)*		
140. **Correspondence received** *(from whom, what and when)*		
141. **Notes:**		