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# **Clinical effectiveness of very low energy diets in the management of weight loss: a systematic review and meta-analysis of randomized controlled trials**

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## Appendices

### Sample search strategy (Medline)

1. Very low calorie diet.ab,hw,kw,ot,sh,ti.
2. Very low energy diet.ab,hw,kw,ot,sh,ti.
3. Vlcd.ab,hw,kw,ot,sh,ti.
4. Vled.ab,hw,kw,ot,sh,ti.
5. Very-low-calorie.ab,hw,kw,ot,sh,ti.
6. Very-low-energy.ab,hw,kw,ot,sh,ti.
7. Very low calorie.ab,hw,kw,ot,sh,ti.
8. Very low energy.ab,hw,kw,ot,sh,ti.
9. Very-low-calorie diet.ab,hw,kw,ot,sh,ti.
10. Very-low-energy diet.ab,hw,kw,ot,sh,ti.
11. Cambridge diet.ab,hw,kw,ot,sh,ti.
12. Lighterlife.ab,hw,kw,ot,sh,ti.
13. Diet.ab,hw,kw,ot,sh,ti.
14. Diets.ab,hw,kw,ot,sh,ti.
15. "Obes\*".ab,hw,kw,ot,sh,ti.
16. Overweight.ab,hw,kw,ot,sh,ti.
17. Weight loss.ab,hw,kw,ot,sh,ti.
18. Dieting.ab,hw,kw,ot,sh,ti.
19. "Lighter life".ab,hw,kw,ot,sh,ti.
20. weight change.ab,hw,kw,ot,sh,ti.
21. 13 or 14 or 15 or 16 or 17 or 18 or 20
22. nutrilett.ab,hw,kw,ot,sh,ti.
23. modifast.ab. or modifast.ot. or modifast.sh. or modifast.ti.
24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 19 or 22 or 23
25. 21 and 24

## Supplementary tables and figures

**Table S1:** Excluded full papers

<b>Paper</b>	<b>Grounds for exclusion</b>
Lantz 2003 (1)	Intermittent VLED
Ryttig 1995 (2)	Intermittent VLED
Wing 1984 (3)	Intermittent VLED
Viegener 1990 (4)	Intermittent VLED
Torgerson 1999 (5)	VLED in comparator arm
Wadden 1985 (6)	VLED in comparator arm
Snel 2011 (7)	VLED in comparator arm
Snel 2012 (8)	VLED in comparator arm
Pavlou 1989 (9)	VLED in comparator arm
Rossner 1998 (10)	VLED in comparator arm
Dixon 2012 (11)	Surgical comparator
Andersen 1987 (12)	Surgical comparator
Gripeteg 2010 (13)	Weight maintenance
Lecheminant 2005 (14)	Weight maintenance
Wikstrand 2010 (15)	Non-randomized study
Murray 2010 (16)	Non-randomized study
Christensen 2010 (17)	Non-randomized study
Richelsen 2007 (18)	Non-randomized study
Mathus-Vliegen 2005 (19)	Non-randomized study
Kajaste 2004 (20)	Non-randomized study
Zahouani 2003 (21)	Non-randomized study
Kaukua 2003 (22)	Non-randomized study
Melin 2003 (23)	Non-randomized study
Paisey 1998 (24)	Non-randomized study
Andersen 1992 (25)	Non-randomized study
Apfelbaum 1999 (26)	Non-randomized study
Paisey 2002 (27)	Non-randomized study
Wadden 1997 (28)	Non-randomized study
Capstick 1997 (29)	Non-randomized study
Agras 1996 (30)	Non-randomized study
Kamrath 1992 (31)	Non-randomized study
Sikand 1988 (32)	Non-randomized study
Finer 1989 (33)	Non-randomized study
Shovic 1993 (34)	Non-randomized study
Miura 1989 (35)	Non-randomized study
Anderson 2001 (36)	Review article
Tsai 2006 (37)	Review article
Kreitzman 1989 (38)	Review article
Lin 2009 (39)	Follow-up less than 12 months
Kaukua 2002 (40)	Follow-up less than 12 months
Arai 1992 (41)	Follow-up less than 12 months
Foster 1990 (42)	Follow-up less than 12 months
Foster 1992 (43)	Follow-up less than 12 months
Inoue 1989 (44)	Follow-up less than 12 months
Toubro 1997 (45)	Authors unable to provide data requested
Simonen 2000 (46)	Authors unable to provide data requested
Wadden 1989 (47)	Authors unable to provide data requested
Rolland trial protocol 2011 (48)	Authors unable to provide data requested
Bliddal 2011 (49)	VLED contained more than 800kcal/day

**Table S2:** Summary of study characteristics

Study ID	Location	Population	Intervention	Comparator	Outcomes reported during study	Follow Up and % completers
<b>Pekkarinen 1997 (50)</b>	Finland	N=59, morbidly obese, 57.8% F	Dietta Mini, liquid meal and vegetables for 6-8 weeks, 500Kcal/day  Low energy food from 14 weeks  Behavioural therapy for 16 weeks	Behavioural therapy for 16 weeks	Weight change, 5% weight loss, 10% weight loss, 20% weight loss, SCL-90 GSI scores, dietary adherence, adverse effects	4, 60 months.  Completers: 44% comparator, 50% intervention at 60 months.
<b>Purcell 2014 (51)</b>	Australia	N=200, obese, 74.5% F	Optifast meal replacements, 450-800kcal/day for 12 weeks (replacing meals) then individualised diet for weight maintenance, if regain changed to 400-500kcal/day deficit diet up to 144 weeks.  Behavioural therapy every 2 weeks (6 sessions) and then every 12 weeks for 144 weeks.	400-500kcal/day deficit diet for 36 weeks with 1 or 2 meals replaced by Optifast a day. Then maintenance as intervention up to 144 weeks.  Behavioural therapy every 2 weeks (18 sessions) and then every 12 weeks for 144 weeks.	Weight change, fasting gherlin and leptin levels, subjective appetite, change in physical activity levels, fat mass, fat free mass, hip circumference and waist circumference 3- $\beta$ -hydroxybutyrate levels, adverse events	12 weeks-rapid group, 36 weeks-gradual group), 144 weeks -both groups, (data from authors at 48 and 108 weeks).  Completers: 44% comparator, 64% intervention at 48 weeks.  Completers: 28% comparator, 52% intervention at 108 weeks.
<b>Rolland 2009 &amp; 2010 (52, 53)</b>	UK	N=72, obese, 84% F	600kcal/day deficit diet and lifestyle advice for 9 months initially and failed to lose >5% body weight  Lighterlife, food replacements for 3-9 months, 550Kcal/day  Behavioural therapy with weekly group sessions  Constant support via email and telephone	600kcal/day deficit diet and lifestyle advice for 9 months initially and failed to lose >5% body weight  Low calorie high protein (800-1500 kcal/day, $\leq$ 40g carbohydrate/ day) Constant support via email and telephone	Weight change, body composition, waist circumference, BP, lipids, electrolytes, eGFR, fasting glucose, fasting insulin, HbA1c, bilirubin, albumin	3, 9 and 24 months.  Completers: 26% comparator, 29% intervention at 24 months.

<b>Rossner 1997 (54)</b>	Norway	N=93, obese, 68% F	Nutrilett, food substitutes for 6 weeks  Booster for 2 weeks at 27 weeks  1) 420Kcal/day 2) 530Kcal/day  HCD between VLED and after VLED up to 52 weeks.  Behavioural support sessions, from 26-52 weeks	LCD (880kcal/day) for 6 weeks  Booster for 2 weeks at 27 weeks  HCD between LCD and after LCD up to 52 weeks.  Behavioural support sessions, as per intervention arm	Weight change, % body fat, waist circumference, hip circumference, WHR, sagittal diameter, ECG, BP*, lipids*, glucose*, adverse effects	1,6 and 12 months.  Completers: 55% comparator, 70% intervention 420kcal, 59% intervention 530kcal at 12 months.
<b>Ryttig 1997 (55)</b>	Sweden	N=81, obese, 54.3% F	Nutrilett, liquid, for 2 months, 420Kcal/day  1 week transition then balanced deficit diet to 1600kcal/ day for 26 months  Behavioural therapy for 26 months (weekly for first month, then every fortnight for second month, monthly for months 3-9 and every 7 weeks for months 10-26)	Balanced deficit diet with 1600kcal/day for 26 months  Behavioural therapy for 26 months as intervention	Weight change, % body fat loss, waist circumference, BP, HR, ECG, electrolytes, glucose, cholesterol, urine ketone body, adverse effects	2, 8, 12 and 24 months.  Completers: 78% comparator, 74% intervention at 12 months.  Completers: 59% comparator, 48% intervention at 24 months.
<b>Stenius 2000 (56)</b>	Finland	N=38, obese, asthma, 76.3% F	Nutrilett, liquid for 8 weeks, 420Kcal/day  Transition period over 8 weeks and then 500-1000 kcal/ day deficit diet  Behavioural therapy group weekly for 12 weeks	Behavioural therapy group weekly for 12 weeks	Weight change, PEF**, FVC, FEV1, QoL (SGRQ), asthma symptoms, acute episodes and use of oral steroids	3 and 12 months.  Completers: 100% comparator, 100% intervention at 12 months.
<b>Torgerson 1997 &amp; Lantz 2003 (57, 58)</b>	Sweden	N=113, obese, 65.5% F	Modifast, liquid for 12 weeks, 456-608Kcal/day  1200-1400kcal/ day (female) or 1400-1800kcal/ day (male) diet for 21 months  Behavioural therapy 59 sessions over 4 years	1200-1400kcal/day (female) or 1400-1800kcal/day (male) diet for 21 months  Behavioural therapy 56 sessions over 4 years	Weight change, 5% weight loss, 10% weight loss, adverse effects	3, 6, 12, 18, 24 and 48 months.  Completers: 91% comparator, 88% intervention at 12 months.  Completers: 47% comparator,

						50% intervention at 48 months.
<b>Tuomilehto 2009 &amp; 2010 (59, 60)</b>	Finland	N=81, overweight, mild OSA, 26.35% F	<p>Modifast, Natrifast or Naturdiet for 12 weeks, 600-800Kcal/day</p> <p>Followed by fat restriction diet (no more than 30% total energy)</p> <p>Behavioural support 14 sessions over 12 months (6 during VLED phase)</p>	Brief intervention on diet and exercise given at baseline, 3 and 12 months.	Weight change, waist circumference, HR, lipids, BP, fasting glucose, fasting insulin, oxygen saturation, AHI **, ESS, SOS, QoL, number of witnessed apnoea, adverse effects	<p>3, 12 and 24 months.</p> <p>Completers: 90% comparator, 88% intervention at 12 months.</p> <p>Completers: 88% comparator, 88% intervention at 24 months.</p>
<b>Wadden 1986 &amp; 1988 (61, 62)</b>	USA	N=59, overweight (obese in 1988), 84.7% F	<p>Preceded by 1000-1200kcal/ day diet for 4 wks</p> <p>PSMF for 8 weeks, 400-500Kcal/day</p> <p>Followed by refeeding period for 4 weeks and 8 weeks 1000-1200kcal/ day diet</p> <p>1) VLED only as above</p> <p>2) VLED as above and behavioural therapy over 12 months (11 sessions)</p>	1000-1200kcal/day diet for 6 months and behavioural therapy over 12 months (11 sessions)	Weight change, BDI	<p>6, 12 and 42 months.</p> <p>Completers: 89% comparator, 83% intervention (VLED alone), 74% intervention (VLED+BT) at 12 months.</p> <p>Completers: 83% comparator, 72% intervention (VLED alone), 74% intervention (VLED+BT) at 42 months.</p>
<b>Wadden 1994 (63)</b>	USA	N=49, obese, 100% F	<p>Preceded by 1200kcal/ day diet for 1 week</p> <p>Optifast, liquid for 16 wks, 420Kcal/day</p> <p>Transition period for 5 weeks, followed by 28 weeks 1200kcal/ day diet and then 26 weeks of weight maintenance diet</p>	<p>1200kcal/day diet</p> <p>Behavioural therapy as per intervention arm</p>	Weight change, body composition, % lost 5kg, % lost 10kg, % lost 20kg, BDI, BES	<p>1, 2, 4, 6, 12 and 18 months.</p> <p>Completers: 81% comparator, 82% intervention at 12 months.</p>

			Behavioural therapy weekly for 12 months and then biweekly for 6 months			
<b>Wing 1991 (64)</b>	USA	N=36, obese, T2DM, 75.5% F	<p>Preceded by 1000-1505 kcal/day diet for 4 weeks</p> <p>Optifast, liquid or lean meat for 8 weeks, 400Kcal/day</p> <p>Transition period for 8 weeks and then maintenance diet (1000-1505kcal/day) until week 72</p> <p>Behavioural therapy, 24 sessions</p>	<p>1000-1505kcal/day diet for 20 weeks minimum</p> <p>Remain on calorie deficit until target weight reached and then maintenance programme</p> <p>Behavioural therapy as per intervention arm</p>	Weight change, HbA1c, lipids, fasting insulin, insulin:glucose ratio, PAQ, EBI, adverse effects	<p>5 and 17 months.</p> <p>Completers: 84% comparator, 100% intervention at 17 months.</p>
<b>Wing 1994-1996 (65-67)</b>	USA	N=93, obese, T2DM, 65% F	<p>Optifast, liquid or lean meat for 12 weeks, 400-500Kcal/day, second 12 week phase of VLED after 24 weeks</p> <p>1000-1200kcal/day diet for 12 weeks between VLED phases and after second VLED phase</p> <p>Behavioural therapy weekly for 50 sessions</p>	<p>1000-1200kcal/day diet</p> <p>Behavioural therapy weekly for 50 sessions</p>	Weight change, HbA1c, lipids, fasting glucose, fasting insulin, BP, BDI, adverse effects	<p>3, 12 and 24 months.</p> <p>Completers: 85% comparator, 84% intervention at 12 months.</p> <p>Completers: 77% comparator, 80% intervention at 24 months.</p>

\* At baseline and 6 months only

\*\* Primary outcome

SGRQ – St George's Respiratory Questionnaire, PEF – Peak Expiratory Flow, FVC – Forced Vital Capacity, FEV1 – Forced Expiratory Volume in 1 minute, BDI – Beck Depression Index, ESS – Epworth Sleepiness Scale, SOS – Snore Outcome Survey, AHI – Apnoea Hypnoea Index, PAQ – Paffenberger Activity Questionnaire, EBI – Eating Behaviour Inventory, BES – Binge Eating Scale, WHR – Waist Hip Ratio

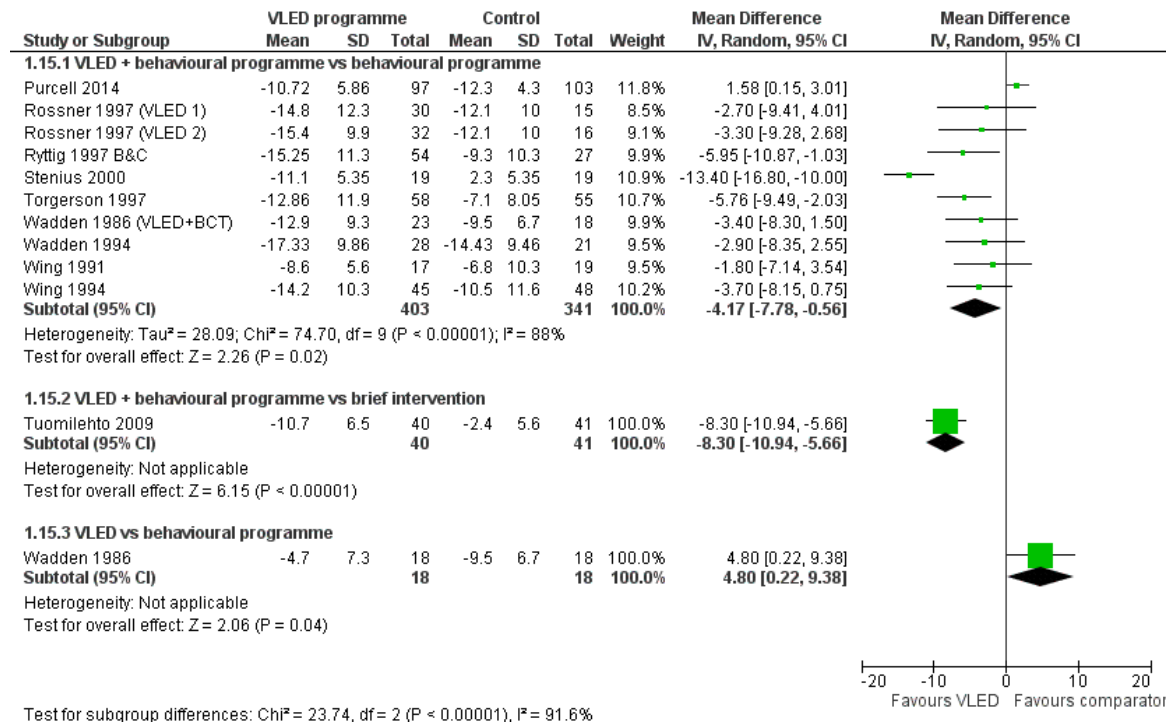


**Table S3:** Risk of bias assessment

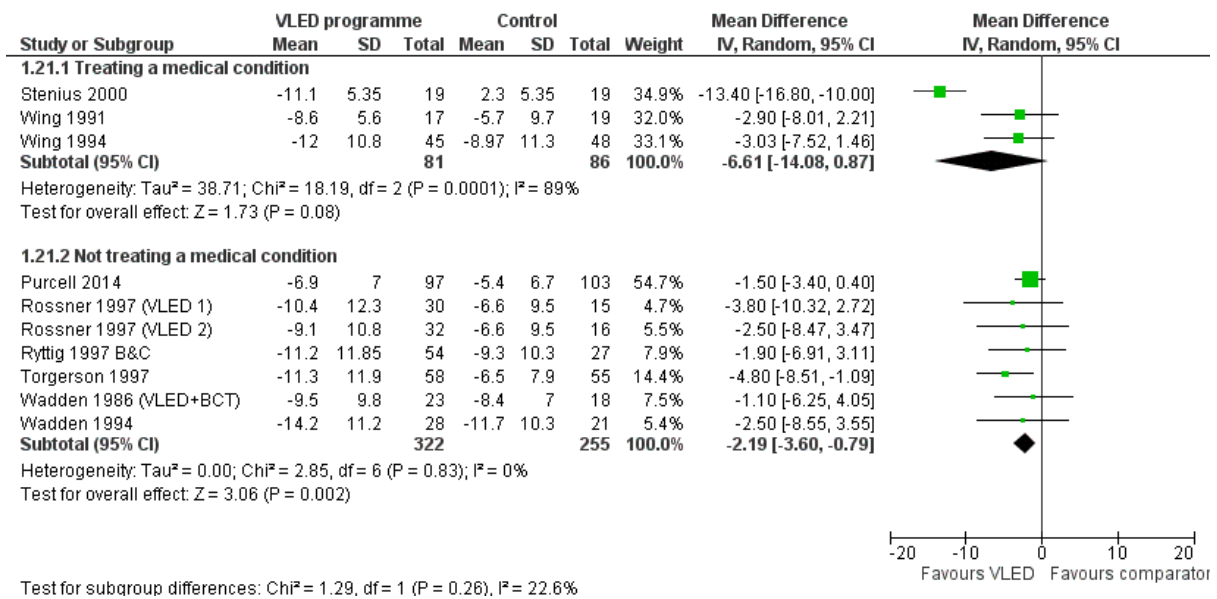
<b>Study ID</b>	<b>Sequence generation</b>	<b>Allocation concealment</b>	<b>Attrition</b>	<b>Selective reporting</b>
Pekkarinen 1997	High	High	Low	Low
Purcell 2014	Low	Low	Low	Low
Ryttig 1997	Unclear	Unclear	Unclear	Low
Wadden 1994	Unclear	Unclear	Low	Low
Wing 1991	Unclear	Unclear	Low	Low
Wing 1994	Unclear	Unclear	Low	Low
Stenius 2000	Unclear	Low	Low	Low
Wadden 1986 and 1988	Unclear	Low	Low	Low
Tuomilieto 2009 and 2010	Low	Low	Low	High
Rolland 2009 and 2010	Unclear	Unclear	Low	Low
Torgerson 1997 and Lantz 2003	Unclear	Low	Low	Unclear
Rossner 1997	Unclear	Unclear	Low	Low

Note that blinding is not reported as it is not possible to blind therapists or participants. Incomplete outcome data are not assessed either because we have addressed this in recalculating the outcomes.

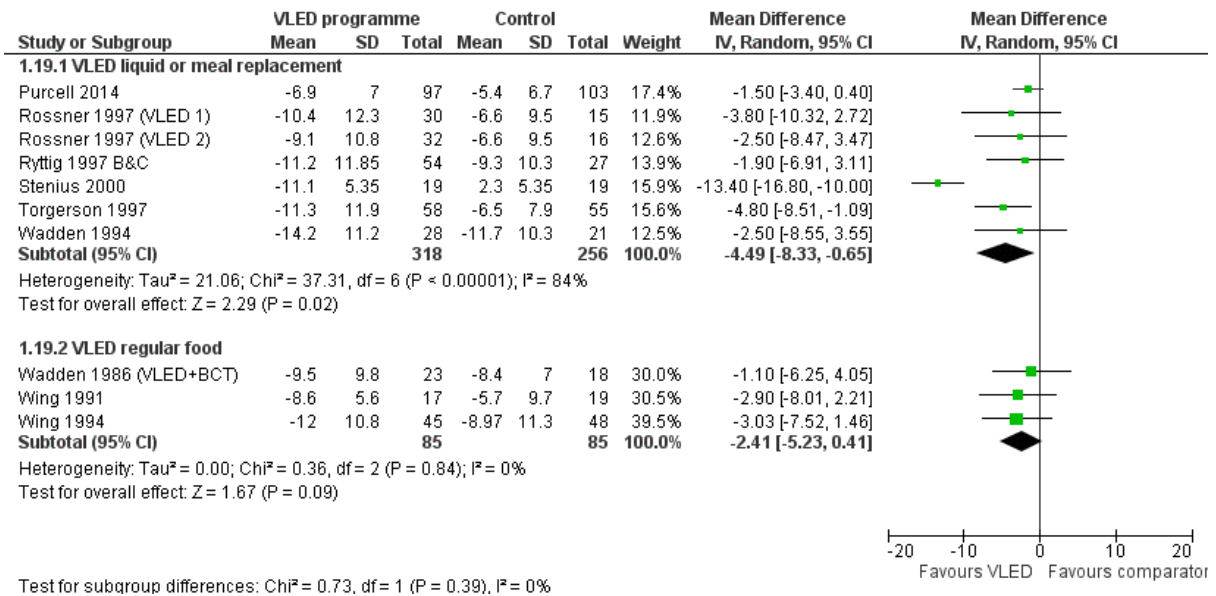
**Figure S1:** Forest plot weight change at 12 months, complete data



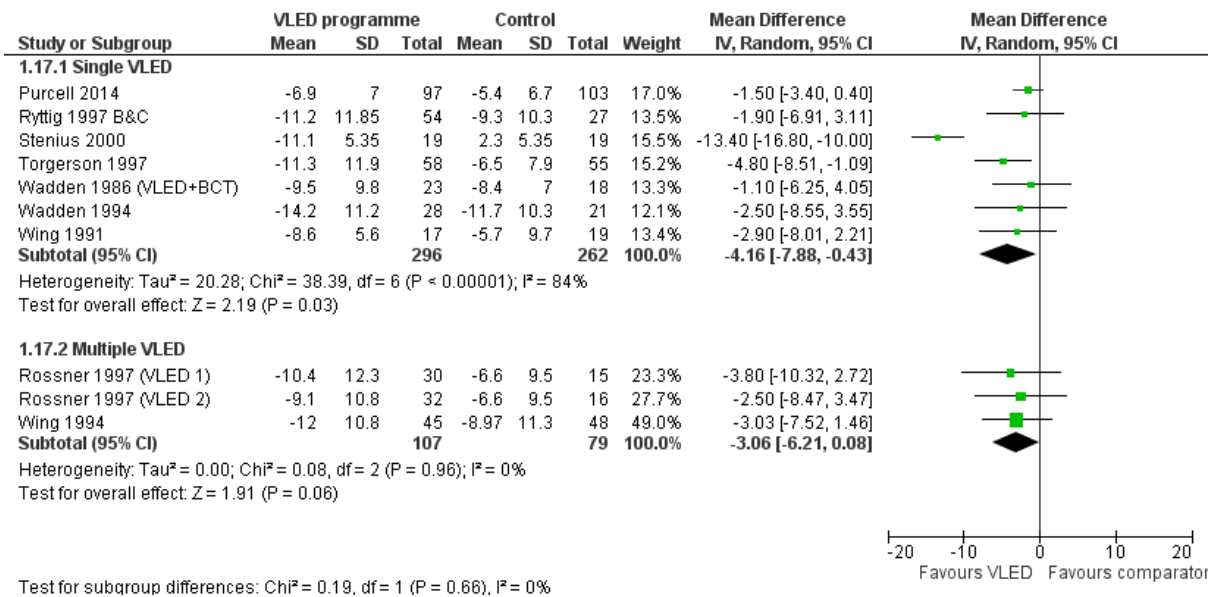
**Figure S2:** Forest plot BOCF weight change at 12 months, subgroups on participant group



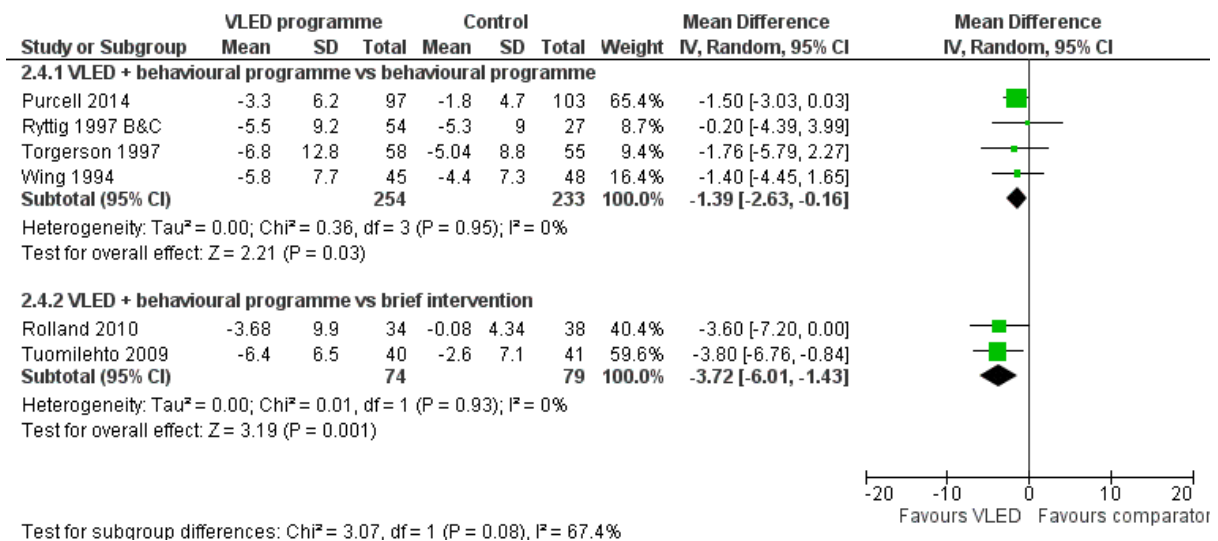
**Figure S3:** Forest plot BOCF weight change at 12 months, subgroups on formulation of VLED



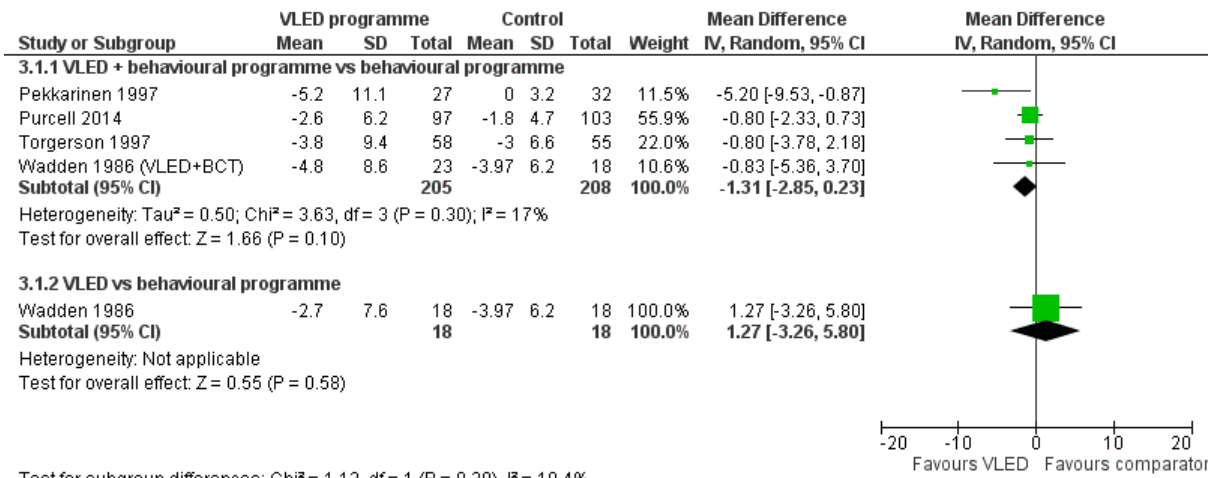
**Figure S4:** Forest plot BOCF weight change at 12 months, subgroups on single or multiple VLED phase



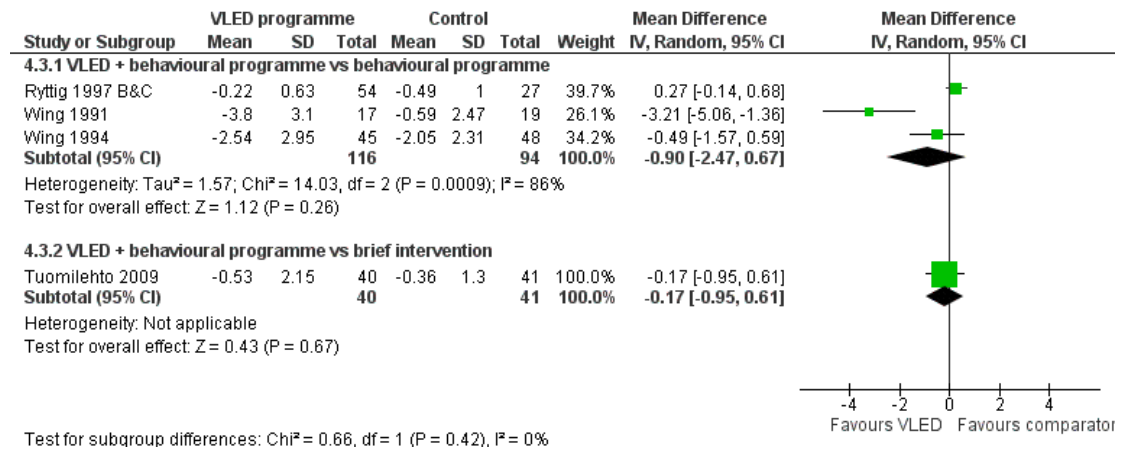
**Figure S5:** Forest plot BOCF weight change at 24 months



**Figure S6:** Forest plot BOCF weight change at 38-60 months

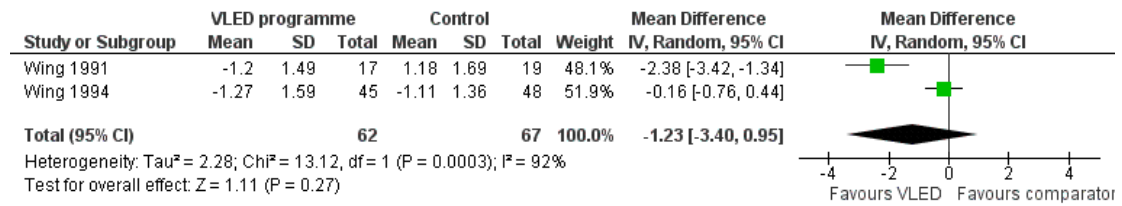


**Figure S7:** Forest plot fasting glucose at 12 months (BOCF)

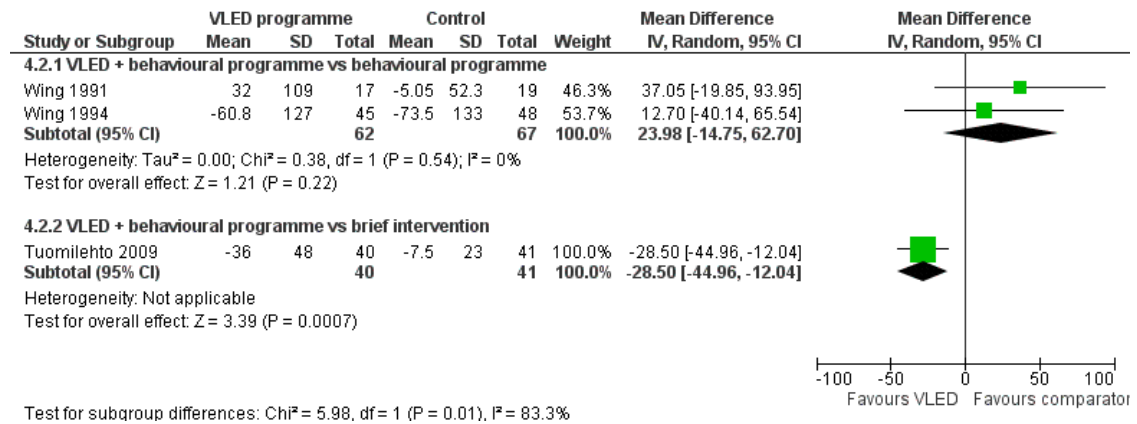




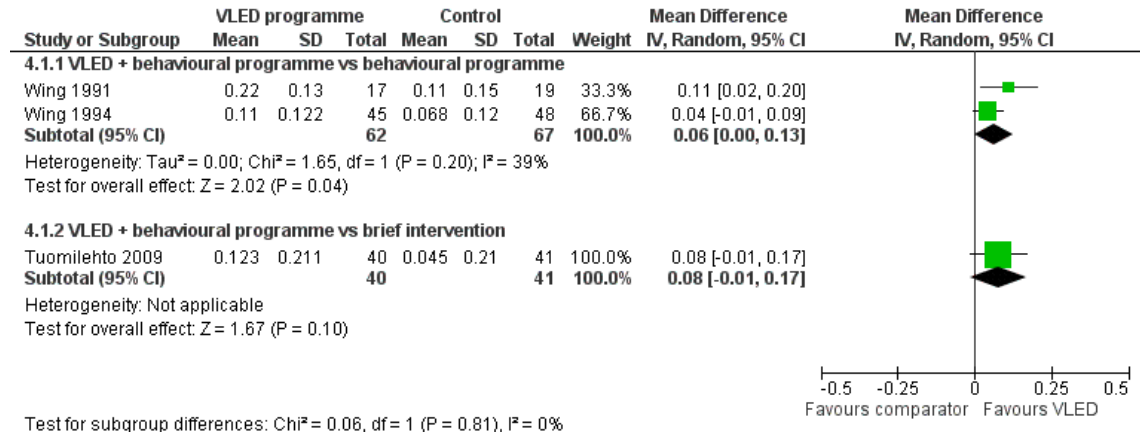
**Figure S8:** Forest plot HbA1c at 12 months (BOCF)



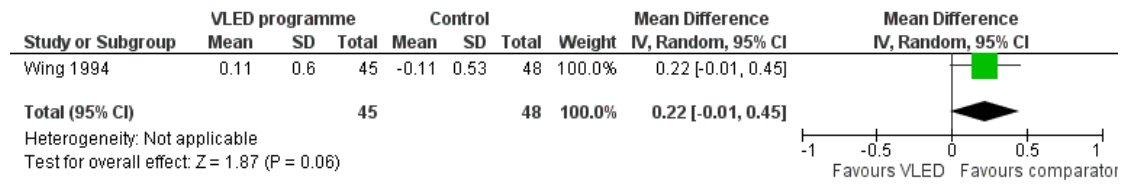
**Figure S9:** Forest plot fasting insulin at 12 months (BOCF)



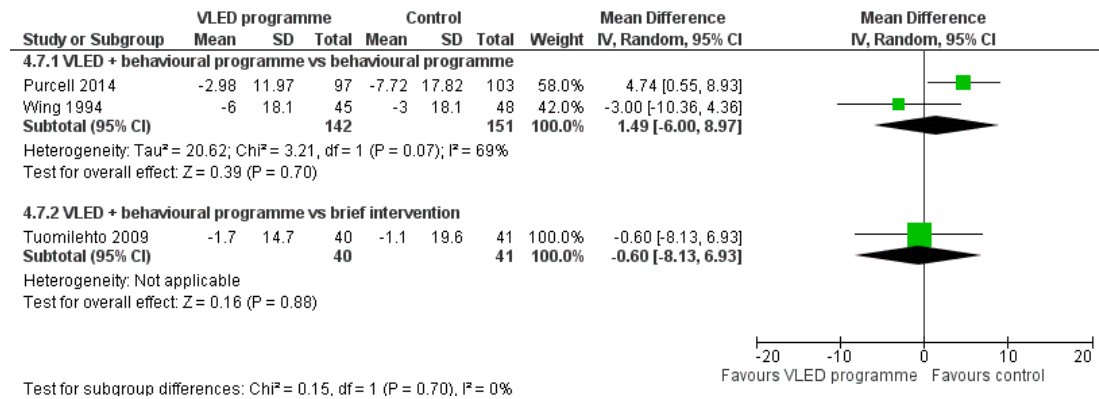
**Figure S10:** Forest plot HDL at 12 months (BOCF)



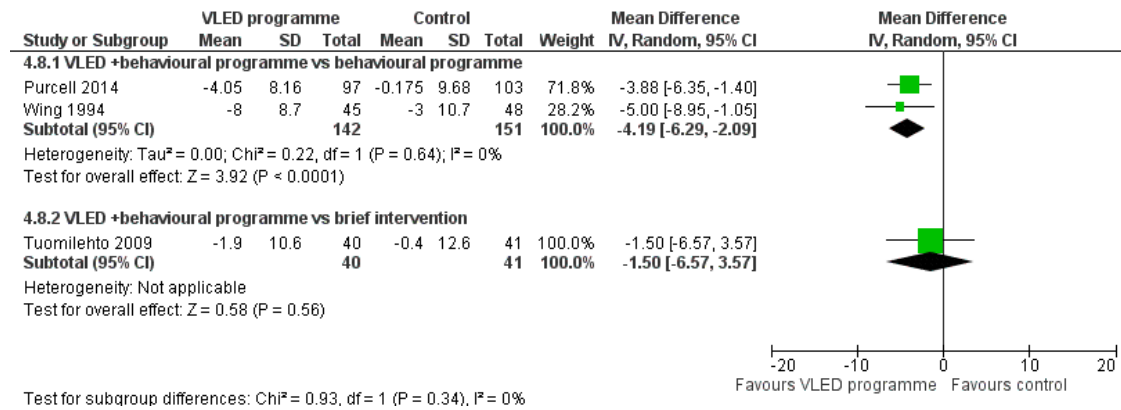
**Figure S11:** Forest plot LDL at 12 months (BOCF)



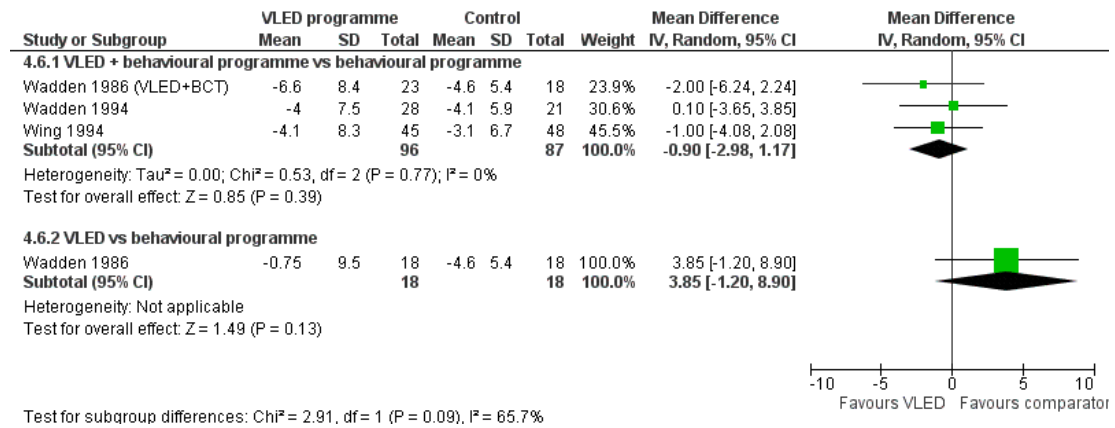
**Figure S12: Forest plot systolic BP at 12 months (BOCF)**



**Figure S13:** Forest plot diastolic BP at 12 months (BOCF)



**Figure S14: Forest plot BDI at 12 months (BOCF)**



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