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Digital Health

Supplementary appendix

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SUPPLEMENTARY MATERIAL

Efficacy of telemedicine for the management of cardiovascular disease: a systematic review and meta-analysis

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Short Title: Telemedicine and cardiovascular disease

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Appendix 1: Search Strategy (PubMed example shown).

1. ((((((Cardiovascular disease[Title/Abstract]) OR (CVD[Title/Abstract])) OR (myocardial infarction[Title/Abstract])) OR (MI[Title/Abstract])) OR (cardiac rehabilitation[Title/Abstract])) OR (coronary[Title/Abstract])) OR (heart[Title/Abstract])
2. (((((((((((((((digital health[Title/Abstract]) OR (mobile health[Title/Abstract])) OR (mHealth[Title/Abstract])) OR (eHealth[Title/Abstract])) OR (web[Title/Abstract])) OR (internet[Title/Abstract])) OR (telemedicine[Title/Abstract])) OR (biosensor[Title/Abstract])) OR (remote monitoring[Title/Abstract]))) OR (wearable[Title/Abstract])) OR (artificial intelligence[Title/Abstract])) OR (AI[Title/Abstract])) OR (virtual care[Title/Abstract])) OR (online[Title/Abstract])) OR (information technology[Title/Abstract])
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7. ((conventional management[MeSH Terms]) OR (standard treatment[MeSH Terms])) OR (non-digital health intervention[MeSH Terms])
8. (((((((((((((((CVD events[MeSH Terms]) OR (hospitalization[MeSH Terms])) OR (morbidity[MeSH Terms])) OR ("mortality"[MeSH Terms])) OR (Framingham score[MeSH Terms])) OR (risk factor modification[MeSH Terms])) OR (blood pressure[MeSH Terms]))

OR ("glucose"[MeSH Terms]) OR (lipid[MeSH Terms]) OR (weight[MeSH Terms]) OR (BMI[MeSH Terms]) OR ("medication adherence"[MeSH Terms]) OR (quality of life[MeSH Terms]) OR (cost[MeSH Terms]) OR ("smoking"[MeSH Terms]) OR (physical activity[MeSH Terms])

9. (#1) OR (#5)

10. (#2) OR (#6)

11. (#3) OR (#7)

12. (#4) OR (#8)

13. (((#9) AND (#10)) AND (#11)) AND (#12)

Appendix 2: Summary of secondary prevention cardiovascular disease studies.

Author (Year)	Country	Study Design	Total (N)	Subject Characteristics (Age in years, Gender)	Duration (months)	Telemedicine (n)	Telemedicine Intervention	WHO Classification	Key Findings
Avila (2018) ¹	Belgium	Randomized controlled trial	90	Mean age (SD) = 61.2 (7.6) Male (n=80)	3	30	Email, telephone consultations, data monitoring (HR)	Consultations between remote patient and healthcare provider Remote monitoring of patient health or remote monitoring of diagnostic data by provider	A telemedicine guided physical fitness programme for patients with coronary artery disease was associated with increased peak oxygen uptake, but no significant changes in body mass index, lipids and other risk factors.
Bhavani (2018) ²	India	Randomized controlled trial	254	Mean age (SD) = 39.0 (14.0) Male (n=146)	12	139	Smartphone-connected mHealth device (pocket ECG, BP, SPO2, activity monitoring, portable brain natriuretic peptide laboratory testing)	Remote monitoring of patient health or remote monitoring of diagnostic data by provider	For these patients with structural heart disease, there was a shorter time to referral for valvuloplasty, lower risk of a composite of hospitalisation or mortality in the telemedicine group assessed with a pocket echocardiography device compared to controls.
Blasco (2012) ³	Spain	Randomized controlled trial	203	Mean age (SD) = 60.8 (11.8) Male (n=163)	12	102	SMS consultation, web-based application, data monitoring (BP, HR, weight, glucose and lipids)	Consultations between remote patient and healthcare provider Remote monitoring of patient health or remote monitoring of diagnostic data by provider	The telemonitoring intervention group had improvements in achieved BP and HbA _{1c} treatment goals, with reductions in body mass compared to control groups. No differences were achieved in smoking cessation or lipids.
Devi (2014) ⁴	UK	Randomized controlled trial	94	Mean age (SD) = 66.2 (9.2) Male (n=70)	6	48	Interactive web-based intervention	Consultations between remote patient and healthcare provider	Intervention improvements noted in energy expenditure, duration of sedentary and moderate activity, reductions of weight, and angina frequency at 6 weeks follow-up compared to controls, but more limited improvements persisted to 6 months.

Frederix (2015) ⁵	Belgium	Randomized controlled trial	80	Mean age (SD) = 60.5 (9.8) Male (n=66)	4.5	40	Email, SMS, data monitoring from motion sensor (blood lipid profile, glycaemic control, waist circumference)	Consultations between remote patient and healthcare provider Remote monitoring of patient health or remote monitoring of diagnostic data by provider	A telemonitoring intervention group within a cardiac rehabilitation setting achieved improvements in oxygen uptake capacity compared to controls, but no significant change was noted in hospitalisation risk.
Reid (2012) ⁶	Canada	Randomized controlled trial	223	Mean age (SD) = 56.4 (9.0) Male (n=188)	12	115	Email consultation, website, data monitoring via pedometer (steps/day)	Consultations between remote patient and healthcare provider Remote monitoring of patient health or remote monitoring of diagnostic data by provider	An internet-based tailored physical activity telemedicine system with guided advice increased objectively measured and self-reported physical activity compared to controls.
Rosario (2018) ⁷	Australia	Randomized controlled trial	66	Age range= 42.0-86.0 Male (n=42)	3.5	33	Data monitoring via mHealth smartphone (BP, weight)	Remote monitoring of patient health or remote monitoring of diagnostic data by provider	A telemedicine addition to cardiac rehabilitation was associated with greater physical participation and completion of the rehabilitation programme, but no changes in risk factors compared to controls.
Sankaran (2019) ⁸	Belgium	Randomized controlled trial	32	Mean age (SD) = 60.9 (8.2) Male (n=24)	4	16	Data monitoring via app for cardiac rehabilitation (physical activity)	Remote monitoring of patient health or remote monitoring of diagnostic data by provider	A telemedicine rehabilitation programme was associated with improvements in glycated haemoglobin, lipids and maximal oxygen capacity compared to controls in this small randomised study.
Southard (2003) ⁹	USA	Randomized controlled trial	104	Mean age (SD) = 62.3 (10.6) Male (n=78)	6	53	Internet-based case management system	Consultations between remote patient and healthcare provider	A telemedicine enhanced cardiac rehabilitation programme was associated with greater weight loss compared to controls, but other measures were not significantly different.
Thorup (2016) ^{10*}	Denmark	Randomized controlled trial	64	Mean age (SD) = 62.8 (11.5)	12	64	Tablet, data monitoring (BP, pulse rate, weight,	Remote monitoring of patient health or remote monitoring	Increased mean (SD) walking steps per day from 5191 (3198) to 7890 (2629) among

				Male (n=51)			daily steps)	of diagnostic data by provider	cardiacpatients with remote monitoring; notably more among younger patients with better adherence to the pedometer.
Varma (2014) ¹¹	USA	Randomized controlled trial	1450	Mean age (SD) = 63.5 (12.6) Male (n=969)	15	908	Data monitoring for implantable cardioverter defibrillator	Remote monitoring of patient health or remote monitoring of diagnostic data by provider	Remote monitoring of implantable cardiac devices associated with no change in all-cause mortality compared to conventionally managed patients, but did achieve reduced in-hospital device adjustments.
Vernooij (2012) ¹²	The Netherlands	Randomized controlled trial	330	Mean age (SD) = 59.9 (8.4) Male (n=246)	12	155	Internet consultation, data monitoring (BP, weight, smoking status, cholesterol)	Consultations between remote patient and healthcare provider Remote monitoring of patient health or remote monitoring of diagnostic data by provider	Reduction (-14%) in the Framingham heart risk score, LDL-C and smoking in the telemedicine intervention group compared with the usual care group.
Wister (2007) ^{13**}	Canada	Randomized controlled trial	296	Mean age (SD) = 56.9 (5.1) Male (n=204)	12	153	Telehealth counselling	Consultations between remote patient and healthcare provider	No changes in outcome variables including blood pressure and Framingham risk scores were found for secondary prevention patients receiving a telemedicine intervention compared to controls.
Wolf (2016) ¹⁴	Sweden	Randomized controlled trial	199	Mean age (SD) = 60.0 (10.0) Male (n=144)	6	94	Website, data monitoring via ehealth diary and symptom tracking tool	Remote monitoring of patient health or remote monitoring of diagnostic data by provider	Improvement in a composite primary endpoint including hospitalisation and death among the person-centred telemedicine group admitted to hospital with acute coronary syndrome, compared to controls.
Zutz (2007) ¹⁵	Canada	Randomized controlled trial	15	Mean age (SD) = 58.5 (8.4) Male (n=12)	3	8	Internet-based consultation for cardiac rehabilitation	Consultations between remote patient and healthcare provider	Very small study assessing virtual cardiac rehabilitation programme, with those participating achieving similar improvements in lipids and exercise capacity to historical controls from a conventional rehabilitation programme.

Ades (2000) ¹⁶	USA	Non-randomized controlled trial	133	Mean age (SD) = 56.8 (10.2) Male (n=108)	3	83	Conference call, data monitoring via trans telephonic	Consultations between remote patient and healthcare provider Remote monitoring of patient health or remote monitoring of diagnostic data by provider	Telemedicine cardiac rehabilitation programme associated with similar changes in oxygen capacity, but an increase in body weight compared to usual rehabilitation.
Macedo (2016) ¹⁷	Brazil	Cohort study	376	Mean age (SD) = 59.0 (11.6) Male (n=276)	24	376	Internet for teleconsultation, discussion of clinical cases via teleconferencing	Consultations between remote patient and healthcare provider Consultations for case management between healthcare providers	The use of chest pain protocols with access to telemedicine was associated with a greater use of a pharmacoinvasive strategy and a trend toward lower in-hospital mortality compared to patients from before the introduction of the new protocols.
Parahuleva (2017) ¹⁸	Germany	Cohort study	364	Mean age (SD) = 65.5 (N/A) Male (n=278)	72	217	Data monitoring of cardiac implantable electronic devices	Remote monitoring of patient health or remote monitoring of diagnostic data by provider	Home monitoring of implantable cardiac devices was associated with fewer treatment-related adverse events compared to standard managed patients.
Wong (2016) ¹⁹	Singapore	Cohort study	492	Mean age (SD) = 59.0 (10.3) Male (n=393)	12	395	Telephone consultation	Consultations between remote patient and healthcare provider	A nurse-led telephone-based care coordination and management intervention in patients post-coronary intervention achieved greater target lipid concentrations compared to controls, but there was no difference in rates of cardiovascular hospitalisation.
Ammenwerth (2015) ²⁰	Austria	Cohort study	25	Mean age= 63.0; range= 47.0-89.0 Male (n=24)	12	25	Data monitoring via app in smart phone (BP, weight, glucose)	Remote monitoring of patient health or remote monitoring of diagnostic data by provider	High medication adherence after 4 and 18 weeks of telemonitoring, but without significant changes to blood pressure or heart rate.

Hart (2019) ²¹	Canada	Cohort study	90	Mean age (SD) = 68.9 (9.8) Male (n=48)	6	90	Telephone consultation	Consultations between remote patient and healthcare provider	A nurse-led telemedicine intervention for atrial fibrillation patients was associated with reduced atrial fibrillation related hospital visits compared to those not receiving the intervention.
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*This study also included heart failure patients

**This study also included primary prevention patients

Appendix 3: Summary of primary prevention cardiovascular disease studies.

Author (Year)	Country	Study Design	Total (N)	Subject Characteristics (Age in years, Gender)	Duration (months)	Telemedicine (n)	Telemedicine Intervention	WHO Classification	Key Findings
Appel (2011) ²²	USA	Randomized controlled trial	415	Mean age (SD) = 54.0 (10.2) Male (n=151)	24	277	Telephone consultation, website, email, data monitoring (weight)	Consultations between remote patient and healthcare provider Remote monitoring of patient health or remote monitoring of diagnostic data by provider	Body weight was reduced from baseline for both telemedicine intervention and control groups, without significant difference.
Bennett (2010) ²³	USA	Randomized controlled trial	101	Mean age (SD) = 54.4 (8.1) Male (n=53)	3	51	Web-based intervention with consultation using messaging feature	Consultations between remote patient and healthcare provider	Obese patients randomised to a telemedicine intervention including counselling achieved greater weight loss than controls.
Bennett (2012) ²⁴	UK	Randomized controlled trial	365	Mean age (SD) = 54.6 (10.9) Male (n=115)	24	180	Tele counselling	Consultations between remote patient and healthcare provider	A telemedicine backed intervention for obese patients from socioeconomically disadvantaged backgrounds achieved reductions in body weight greater than controls, but no change in blood pressure was seen.
Broekhuizen (2012) ²⁵	The Netherlands	Randomized controlled trial	340	Mean age (SD) = 45.3 (12.9) Male (n=147)	12	181	Personalised health counselling via web-based and telephone	Consultations between remote patient and healthcare provider	No differences seen in risk markers including lipids between telemedicine-backed lifestyle intervention for patients with familial hypercholesterolaemia and controls.
Claes (2013) ²⁶	Belgium	Randomized controlled trial	314	Mean age (SD) = 40.7 (10.5) Male (n=219)	36	195	Personalised website, consultation via regular mail, email, telephone	Consultations between remote patient and healthcare provider	A remote lifestyle modification programme in addition to medical care did not result in significant differences in lipids, body weight or blood pressure.
Green (2014) ²⁷	USA	Randomized	101	Mean age (SD)	18	51	Web-based dietitian,	Consultations	A remote dietitian intervention

		controlled trial		= 56.9 (7.0) Male (n=59)			communication via electronic health record linked secure messaging	between remote patient and healthcare provider	improved weight loss and blood pressure control compared to usual care, for patients with a high pre-intervention cardiac risk.
Jacobs (2011) ²⁸	Belgium	Randomized controlled trial	287	Mean age (SD) = 40.0 (11.0) Male (n=192)	6	194	Tailored website, one-to-one coaching (email, telephone)	Consultations between remote patient and healthcare provider	The cardiovascular events prevention programme did not alter outcomes compared to control patients.
Kiselev (2012) ²⁹	Russia	Randomized controlled trial	199	Mean age (SD) = 50.0 (11.0) Male (n=110)	12	97	SMS and mobile phone technology	Consultations between remote patient and healthcare provider	Using mobile technology and messaging prompts resulted in improved blood pressure control compared to traditional ambulatory care management.
Mendelson (2014) ³⁰	France	Randomized controlled trial	107	Mean age (SD) = 63.0 (9.0) Male (n=89)	4	54	Telephone consultation, health-related messages via pictogram, smartphone, data monitoring (BP, CPAP adherence, sleepiness and quality of life)	Consultations between remote patient and healthcare provider Remote monitoring of patient health or remote monitoring of diagnostic data by provider	The telemedicine group achieved no improvement in self-measured blood pressure compared to controls for patients with obstructive sleep apnoea managed using continuous positive airways pressure.
Verheijden (2004) ³¹	Canada	Randomized controlled trial	146	Mean age (SD) = 63.0 (10.5) Male (n=111)	8	73	Web-based targeted nutrition counselling and social support	Consultations between remote patient and healthcare provider	Cardiac risk measures including blood pressure and lipids were not different in the telemedicine intervention group receiving web based monitoring and counselling when compared to controls.
Wister (2007) ^{13*}	Canada	Randomized controlled trial	315	Mean age (SD) = 55.4 (5.4) Male (n=131)	12	157	Telehealth counselling	Consultations between remote patient and healthcare provider	Significant changes for the telemedicine treatment group relative to controls in Framingham score, lipids, blood pressure, nutrition level and health confidence.
Park (2012) ³²	Republic of Korea	Quasi-experimental	67	Mean age (SD) = 56.7 (5.6) All females	3	34	Telephone or internet consultation, data monitoring (mobile phone and web-based diary internet)	Consultations between remote patient and healthcare provider	The telemedicine group had reductions in lipids, blood pressure and waist circumference in obese post-menopausal women, when compared to non-

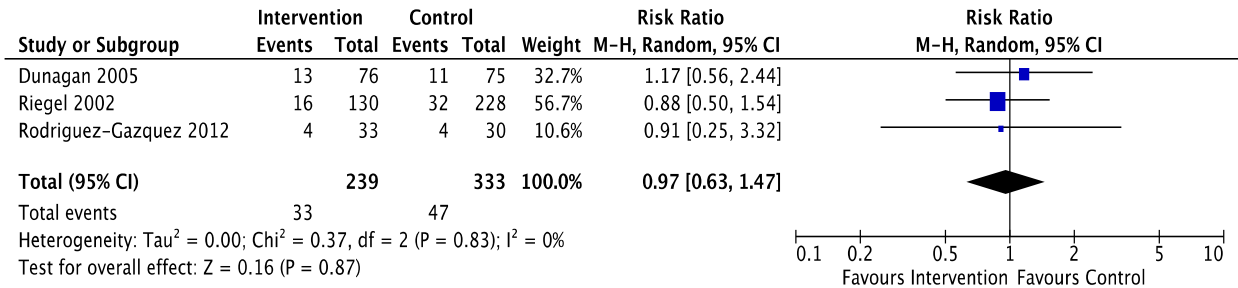
								Remote monitoring of patient health or remote monitoring of diagnostic data by provider	randomised controls.
Randolph (1999) ³³	USA	Cross-sectional	133	Median age 2 days (range 1 to 29 days) Gender (N/A)	N/A	133	Telemedical echocardiograms, case management discussion on the teleechocardiography	Remote monitoring of patient health or remote monitoring of diagnostic data by provider Consultations for case management between healthcare providers	Paediatric study transmitting neonatal echocardiogram images for remote review. Data transfer was felt adequate for diagnosis and medical management was altered in the majority of cases.

*This study also included secondary prevention patients

Appendix 4: Risk of cardiovascular mortality in heart failure studies of remote consultation suitable for meta-analysis.

Remote Consultation for Heart Failure Management

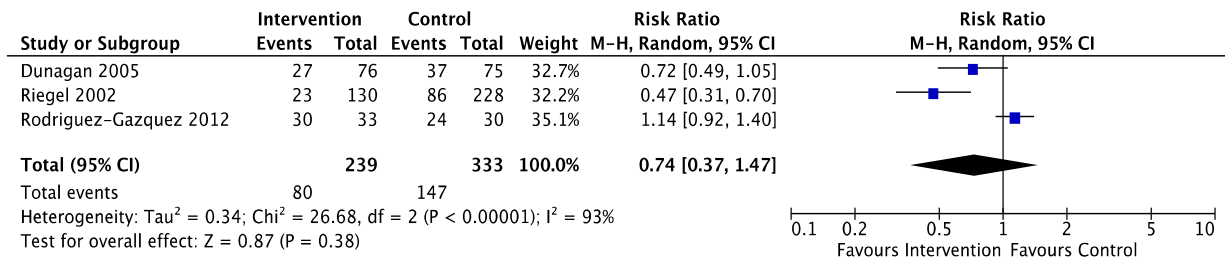
Short-term Follow-up



Appendix 5: Risk of cardiovascular hospitalisation in heart failure studies of remote consultation suitable for meta-analysis.

Remote Consultation for Heart Failure Management

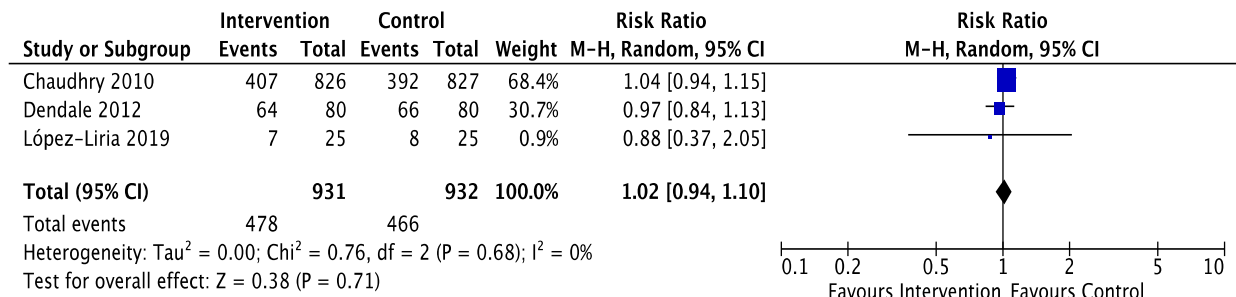
Short-term Follow-up



Appendix 6: Risk of all-cause hospitalisation in heart failure studies suitable for meta-analysis.

Remote Monitoring for Heart Failure Management

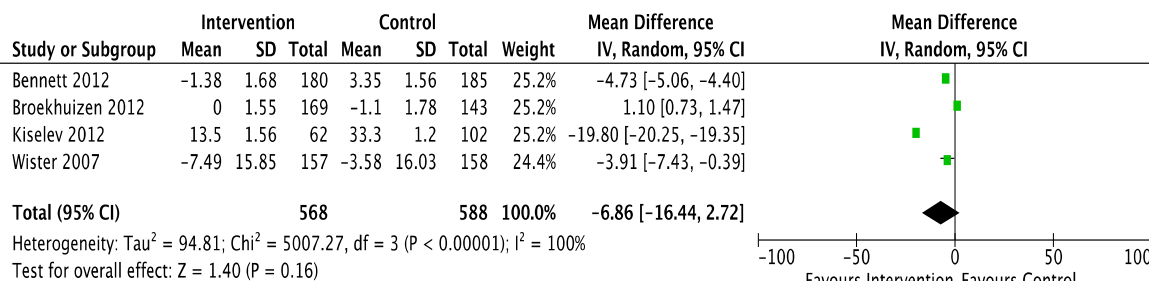
Short-term Follow-up



Appendix 7: Changes in blood pressure and body mass index in studies suitable for meta-analysis.

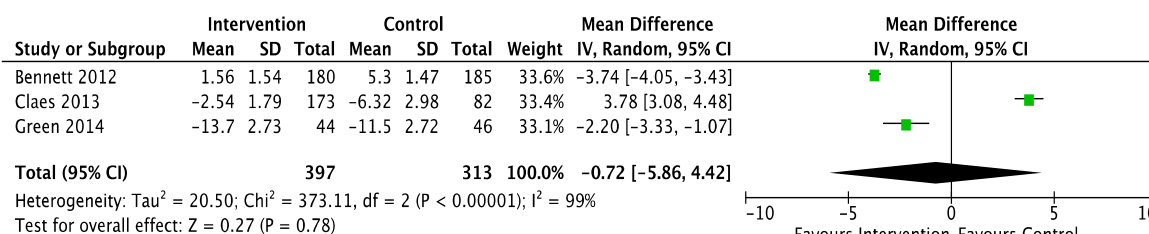
A. Remote Consultation for Primary CVD Prevention (Systolic Blood Pressure)

Short-term Follow-up



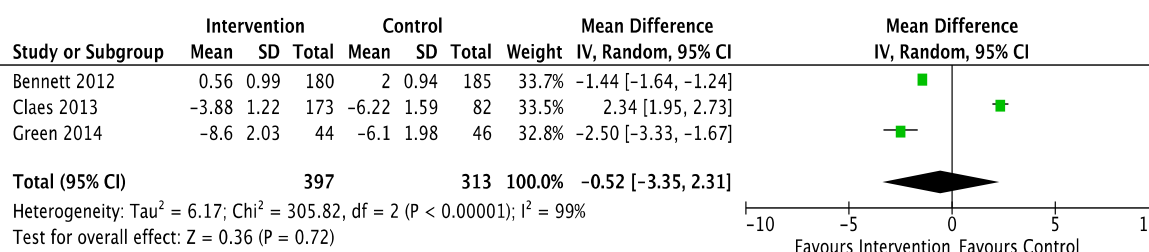
B. Remote Consultation for Primary CVD Prevention (Systolic Blood Pressure)

Long-term Follow-up



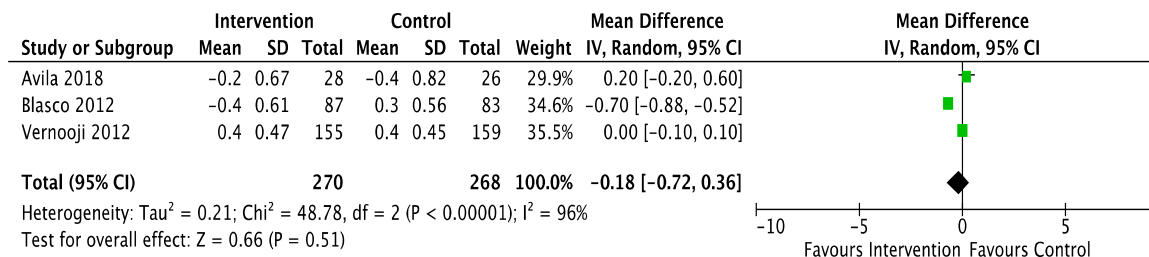
C. Remote Consultation for Primary CVD Prevention (Diastolic Blood Pressure)

Long-term Follow-up



D. Remote Monitoring and Consultation for Secondary CVD Prevention (BMI)

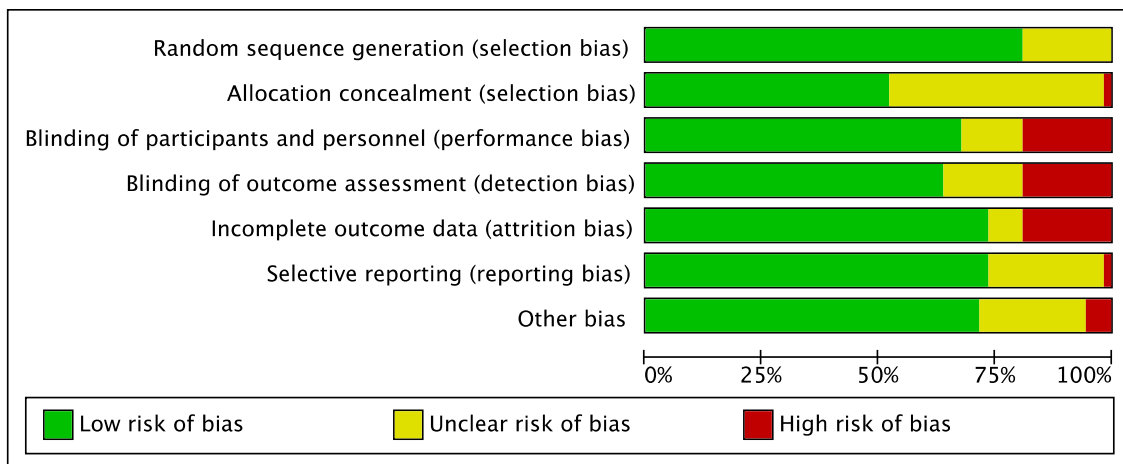
Short-term Follow-up



Appendix 8: Cochrane risk of bias summary per study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Antoniceilli 2008	?	?	●	●	●	?	●
Antoniceilli 2010	?	?	●	●	●	?	●
Appel 2011	●	●	●	●	●	●	●
Avila 2018	●	●	●	●	●	●	●
Bennett 2010	●	●	●	●	●	?	●
Bennett 2012	●	●	●	●	●	●	●
Bhavani 2018	●	●	●	?	●	●	?
Blasco 2012	?	●	●	●	●	?	?
Böhm 2016	●	●	●	●	●	●	●
Boriani 2017	●	●	●	●	?	●	●
Broekhuizen 2012	●	●	●	?	●	●	●
Chaudhry 2010	●	●	●	●	●	●	●
Claes 2013	●	●	●	●	●	●	●
Dendale 2012	●	?	?	?	●	●	●
Devi 2014	●	●	●	●	?	●	●
Dunagan 2005	●	●	●	●	●	?	●
Frederix 2015	●	?	●	●	●	●	●
Frederix 2019	●	●	●	●	●	●	●
Gingele 2019	?	?	?	?	●	●	●
Giordano 2009	●	●	●	●	●	●	●
Green 2014	●	?	●	●	●	?	?
Guédon-Moreau 2013	●	?	●	●	●	●	●
Jacobs 2011	?	?	●	●	●	●	●
Kiselev 2012	?	?	●	●	●	?	●
Koehler 2011	●	?	●	●	●	●	●
Koehler 2018	●	●	●	●	●	●	●
Kotooka 2018	●	●	?	?	●	●	●
Lear 2014	●	●	●	●	●	●	●
López-Liria 2019	●	●	●	●	●	●	?
Lundgren 2016	●	?	●	●	●	?	?
Lüthje 2015	?	?	●	●	●	●	●
Mendelson 2014	●	●	●	●	●	●	●
Morgan 2017	●	?	●	●	●	●	●
Piette 2015	●	?	●	●	●	●	?
Piotrowicz 2015	●	●	●	●	●	?	?
Rahimi 2020	●	●	●	●	●	●	●
Reid 2012	●	●	●	●	●	●	●
Riegel 2002	?	?	●	●	●	?	●
Rodriguez-Gazquez 2012	●	●	?	?	?	●	?
Rosario 2018	●	?	●	●	●	●	?
Sankaran 2019	●	?	●	●	●	●	●
Scherr 2009	?	?	?	?	●	?	?
Southard 2003	●	?	●	●	●	●	●
Tajstra 2020	●	●	●	●	●	●	●
Thorup 2016	●	?	●	●	?	●	●
Varma 2014	●	●	●	●	●	●	●
Verheijden 2004	●	?	●	●	●	●	●
Vernooji 2012	●	●	●	●	●	●	?
Weintraub 2010	●	?	?	●	●	●	●
Wister 2007	●	●	●	●	●	?	●
Wolf 2016	●	?	●	?	●	●	●
Zutz 2007	?	?	?	?	●	?	?

Appendix 9: Cochrane risk of bias graphical summary.

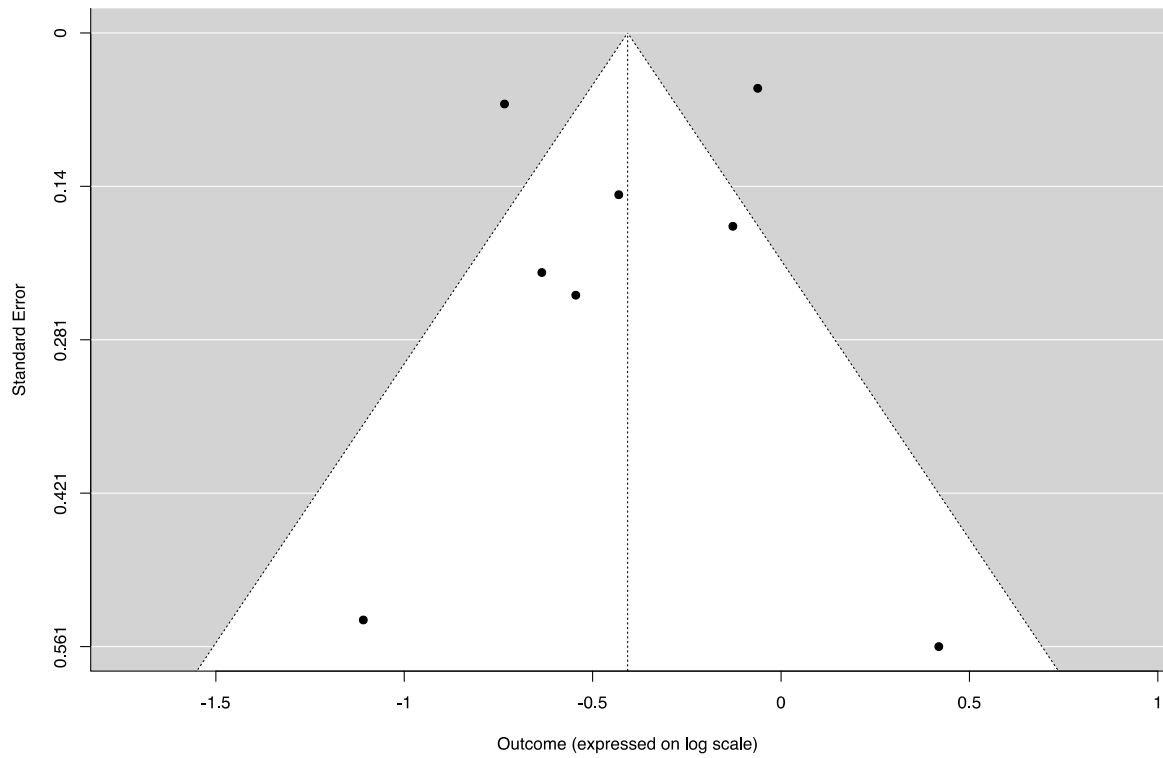


Appendix 10: Newcastle-Ottawa Scale quality assessment.

Study (Year)	Representatives of the exposed cohort (star)	Selection of the nonexposed cohort (star)	Ascertainment of the exposure (star)	Demonstration that outcome of interest was not present at the start of the study (star)	Comparability of cohorts on the basis of the design or analysis controlled for confounders (star)	Assessment of outcome (star)	Was follow-up long enough for outcomes to occur (star)	Adequacy of follow-up of cohorts (star)	Quality
Ades (2000)	1	1	1	0	1	1	1	1	High
Ammenwerth (2015)	1	0	0	0	0	0	1	1	Low
Chen (2010)	1	1	0	1	1	0	1	1	Medium
Dadosky (2018)	1	1	1	1	1	1	0	1	High
Hart (2019)	1	0	0	0	0	0	1	0	Low
Kurek (2017)	1	1	1	0	2	1	1	1	High
Macedo (2016)	1	0	1	1	1	1	1	1	High
Martín-Lesende (2017)	1	0	1	0	0	1	1	0	Medium
Masella (2008)	1	0	1	0	0	1	1	0	Medium
Mittal (2016)	1	1	1	0	0	1	1	1	Medium
Moore (2016)	1	0	1	0	0	0	1	0	Low
Nishii (2015)	1	0	1	1	0	0	1	1	Medium
Odeh (2015)	1	0	1	0	0	1	1	0	Medium
Parahuleva 2017	1	1	1	1	1	1	1	0	High
Park (2012)	1	1	1	0	2	1	1	1	High
Quinn (2006)	1	1	0	1	0	0	1	1	Medium
Randolph (1999)	1	0	1	0	0	1	0	0	Low
Rosen (2017)	1	0	1	0	0	1	1	1	Medium
Scalvini (2006)	1	0	0	0	0	1	1	1	Medium
Wong (2016)	1	1	1	0	1	1	1	1	High

Appendix 11: Publication bias assessment.

Funnel plot to assess for publication bias in studies used for meta-analysis of cardiovascular mortality risk. Egger's tests for plot asymmetry does not support publication bias ($p=0.93$).



References

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