Incidence of diabetes mellitus, cardiovascular outcomes and mortality after a 12-month lifestyle intervention: A 9-year follow-up

Incidence of diabetes mellitus, cardiovascular outcomes, and mortality after a 12-month lifestyle intervention: a 9-year follow-up.

Ponzo V[a], Gentile L[b], Gambino R[a], Rosato R[c], Cioffi I[d], Pellegrini N[e], Benso A[a], Broglio F[a], Cassader M[a], Bo S[a]

[a] Department of Medical Sciences, University of Turin, Turin, Italy

[b] Diabetic Clinic, Hospital of Asti, Asti, Italy.

[c] Department of Psychology, University of Turin, Turin, Italy

[d] Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy

[e] Department of Food and Drug, University of Parma, Parma, Italy

Corresponding author: Simona Bo, Department of Medical Sciences, University of Turin, Corso Dogliotti 14, 10126 Turin, Italy; Telephone +(39)(011)6336036 Fax+(39)(011)6335401 E-mail: simona.bo@unito.it

Abbreviations CVD (Cardiovascular Disease); T2DM (Type 2 Diabetes Mellitus); OGTT (Oral Glucose Tolerance Test); ICD-9 (International Classification of Diseases, Ninth Revision); CRP (C-Reactive Protein); NNT (Number Needed to Treat); HR (Hazard Ratio); CI (Confidence Intervals).

Running title: outcomes after a lifestyle intervention

Word Count: text 1718

Number of references: 13

Number of tables: 1

Trial registered at: www.clinicaltrials.gov (NCT03416439)

Declarations of interest: none

Keywords: cardiovascular diseases, diabetes mellitus, lifestyle intervention, metabolic syndrome, mortality

Lifestyle interventions are known to significantly reduce the incidence of type 2 diabetes mellitus (T2DM) by improving dietary habits and exercise levels, with metabolic benefits persisting up to 20 years, although with a progressive reduction over time [1-3]. Most of these very intensive programs were indeed too expensive to be implemented nationally [4].

Less intensive lifestyle interventions, such as those in the primary health care setting determined lower weight loss, and a favorable impact on metabolic and cardiovascular risk factors in the medium term [5], but the long-term benefits are not known. Furthermore, cardiovascular disease (CVD) incidence and mortality were infrequently reported, thus the knowledge relative to these outcomes is scarce [6].

In 2004, a relatively simple 1-year lifestyle intervention was carried out in in 335 dysmetabolic individuals from a population-based cohort of adults [7]. In the short-term, the intervention induced a modest weight loss, but significantly improved multiple metabolic and inflammatory abnormalities when compared to the usual care by the family physicians [7], and after 4-year follow-up, a better metabolic profile was still evident in the intervention group, even if many of the beneficial effects had disappeared [8].

Our aim was evaluating the impact of the lifestyle intervention on diabetes incidence, all-cause mortality and CVD incidence and mortality, and their combination, after 9-year follow-up.

Subjects with either the metabolic syndrome or 2 components of the syndrome and high-sensitivity C-reactive protein serum (CRP) values ≥3 mg/L, the cutoff value for CVD increased risk, were identified from a population-based cohort of adults, aged 45-64-years [7]. Patients with known diabetes, CVD, chronic liver or kidney disease, or advanced cancer were excluded. Out of 375 subjects, 187 were randomly allocated to the intervention arm and 188 to the control arm; respectively 18 and 22 individuals refused to participate. Therefore, 169 patients were assigned to a lifestyle intervention program carried out by trained professionals (intervention arm) and 166 to standard, unstructured information given by the family physicians (control arm) [7].

This randomized, prospective open trial was approved by the local Ethical Committee; all the patients gave their written informed consent and procedures conformed to the principles of the Helsinki Declaration.

Between October and November 2004, all the subjects received verbal, not-written, information, emphasizing the importance of a healthy lifestyle from their family physicians, who were blinded to the group assignment. These practitioners had previously participated in 3 meetings on standard practice lifestyle recommendations. No further individualized programs were offered to the control arm, and these subjects were reevaluated after 1-year follow-up [7]. From December 2004 to December 2005, the intervention arm received detailed verbal and written individualized diet and exercise recommendations from trained professionals during 5 sessions of at least 60 minutes covering diet, exercise, and behavior modifications. The first session was a one-to-one visit, the following were group sessions based on behavioral counseling and focusing on practical lifestyle tips (reducing high-calorie density foods and saturated fats, increasing high-fiber foods and physical activity, strategies for out-of-home eating and healthful food shopping) [7].

Anthropometric measurements and blood samples were collected from all the participants at the beginning and at the end of the trial. Laboratory methods have been described previously [7].

In 2014, the participants were followed-up by their family physicians. Follow-up data were collected for all participants by the review of the medical records. Information on the vital status and the causes of death of those who died was collected from the demographic files of the town of residence or death.

The primary outcome was the incidence of diabetes; secondary outcomes were all-cause mortality, CVD incidence and mortality, and their combination.

Diabetes was defined in accordance with international guidelines. The diagnosis of CV disease was based on documented events recorded by the family physicians (i.e. angina, myocardial infarction, coronary artery by-pass graft or other procedure to treat coronary artery disease, transient ischemic attack, stroke, gangrene, amputation, vascular surgery, documented peripheral arterial disease).

The underlying cause of death was obtained from the death certificate and coded according to ICD-9 (International Classification of Diseases, Ninth Revision). Deaths due to CVD corresponded to ICD codes 410–414 (coronary artery diseases), 430–438 (strokes), 440 (peripheral artery diseases) and other ICD codes between 390–459 and 798.1 (other CV diseases).

The observational period for outcome incidence was from the trial start to the date of diagnosis, or death, or 31 December 2014.

Person-years were the sum of time under follow-up for all the participants in each arm between the beginning of the study and the occurrence of an outcome event or, alternatively, the end the follow-up period, if the outcome did not develop.

The t-Student test or Mann-Whitney test were used to compare the follow-up variables between the two arms, as appropriate.

Outcome incidence was analyzed through Cox-proportional hazards regression, by estimating the hazard ratio (HR) and its 95 % confidence intervals (CI), after adjusting for age, sex, education level, and, for incident CVD and mortality, for smoking habits.

Separate analyses were performed for diabetes incidence, total mortality, CV mortality and incidence of CV events, and their combination.

The mean total follow-up time was 8.75-years for diabetes, 9.48-years for mortality, and 9.34-years for the combined outcome.

At follow-up, systolic blood pressure, and fasting glucose values were significantly higher in the control group, while neither weight, BMI and lipid values, nor the prevalence of impaired fasting glucose differed between groups (**Table 1**). Indeed, median changes from baseline to follow-up in the values of weight, BMI, blood pressure, fasting glucose, triglycerides, and HDL cholesterol significantly differed between the two arms.

Forty-one participants developed T2DM (**Table 1**). The incidence of T2DM was lower in the intervention arm and the number needed to treat (NNT) to prevent a case of T2DM was 12. Patients

from the intervention arm showed a 53% lower risk of developing diabetes in the regression model, controlled for age, sex and educational level. The control group developed diabetes after a mean of 8.33-years, while the intervention group after 9.17-years; the difference (0.84) corresponded to about 10-months of delayed disease incidence.

During the 9-years follow-up, 49 deaths occurred, 16 of which were attributed to CVD, and there were 20 new CV events (Table 2). The mortality rate was 29% lower in the intervention arm, even if this difference was not statistically significant. There was no significant difference between the intervention and control arms in the rate of new CVD (HR 0.91; 95% CI 0.39-2.29), CVD mortality (0.42; 0.15-1.23), and the combined CV outcome (0.60; 0.29-1.24) but our study had limited statistical power to detect differences for these outcomes.

Data did not change after adjusting for weight and BMI change.

In patients with multiple dysmetabolic conditions, the reduction in diabetes incidence identified at the end of the trial was still present after 9-years in the intervention arm of our low-intensity short-term program, while the usual care provided by family physicians was less effective.

The search for a low-cost, easy-to-apply method is the current challenge in order to counteract the epidemic increase in diabetes, occurring worldwide. Our relatively simple lifestyle program, with a limited number of educational visits, mostly group-sessions, has proved to be as effective as more intensive programs in halving the incidence of diabetes in the long-term, even if our delay in time to diabetes diagnosis was smaller [1-3,9].

Other trials performed in patients with impaired glucose tolerance at baseline showed higher percentage of diabetes development, ranging from 5 to 10% per year [1-3]. Our diabetes incidence rates ranged from 0.90 to 1.95%, but only 60% of our patients had hyperglycemia at baseline, while the remaining participants had other dysmetabolic characteristics. In addition, the use of the oral glucose tolerance test (OGTT) by other trials could have allowed an increased number of diabetes

diagnoses [1-3,5]. Indeed, our results suggested the efficacy of the intervention also in patients with multiple -not exclusively hyperglycemic- metabolic abnormalities.

Differently from other lifestyle trials, but similarly to the Da Quing Study, diabetes reduction was not associated with a considerable weight change, since only a modest weight loss occurred in our intervention arm, and results did not change after adjusting for weight variations during follow-up. Either changes in not-assessed body composition parameters, or persistent metabolic benefits (a sort of metabolic memory) have been hypothesized to explain these apparently counterintuitive results [4].

Indeed, the small weight reduction of our patients, much lower than that obtained by more intensive lifestyle trials [1-3], but comparable to real-life studies [5], should be view as an achievement, considering the usual progressive weight gain of ageing.

We encouragingly found an overall reduction in mortality and CV outcomes, although with wide confidence intervals and without significant results. Even if the small number of events prevents us from drawing conclusions, the persistent favorable changes at follow-up of most CV risk factors in the intervention arm support the possibility of a real benefit on CV outcomes. Other trials failed to identify significant effects on CV outcomes and mortality [6], and only very long follow-up studies, such as the 23-year follow-up of the Da Qing Study, reported a significant reduction in all-cause and CV mortality in women [3].

Power calculation was performed for the original intervention trial [9]; indeed, we estimated that the study achieved a power=86% to detect a 0.47 HR for the incidence of diabetes in the intervention arm *vs* the controls, with a two-tailed α-value=0.05. The low number of events, however, reduced the power of the study to detect difference in the secondary outcomes.

Blinding was not feasible, but endpoints were ascertained by personnel blinded to participant randomization. Follow-up data about diet/exercise habits were not available, therefore if lifestyle changes were maintained beyond the intervention period and have contributed to the differences in

diabetes incidence could not be verified. Cardiorespiratory fitness, which has recently been recognized a major CV prognostic marker [10-12], was not evaluated. We did not perform the OGTT, but used the fasting glucose value, which indeed was shown to be the strongest component linking the metabolic syndrome with incident diabetes [13].

The completeness in the follow-up, due to the involvement of the family physicians, and the relative simplicity of the intervention, which increases the possibility of its replication, were all strengths of the study.

A low-resource short-term program seems to be effective in the long-term in attenuating the risk for diabetes in individuals with multiple dysmetabolic conditions.

Acknowledgments

Funding: This study was supported by a grant from Regione Piemonte 2008

Author contributions

The authors' contributions were as follows:

Valentina Ponzo and Simona Bo: conception and design of the study;

Valentina Ponzo: supervision of data collection;

Luigi Gentile, Roberto Gambino, Iolanda Cioffi, Andrea Benso, and Fabio Broglio: data collection;

Roberto Gambino, Rosalba Rosato, Nicoletta Pellegrini, and Simona Bo: data analysis;

Valentina Ponzo, Luigi Gentile, Roberto Gambino, Rosalba Rosato, Iolanda Cioffi, Nicoletta Pellegrini Maurizio Cassader, and Simona Bo: interpretation of the findings;

Valentina Ponzo and Simona Bo: manuscript writing;

all authors: manuscript revision.

All authors have approved the final version of the manuscript.

References

[1] Lindström J, Peltonen M, Eriksson JG, Ilanne-Parikka P, Aunola S, Keinänen-Kiukaanniemi S, Uusitupa M, Tuomilehto J, Finnish Diabetes Prevention Study (DPS). Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). Diabetologia 2013; 56:284–93.

[2] Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM. Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009; 374:1677-86.

[3] Li G, Zhang P, Wang J, An Y, Gong Q, Gregg EW, Yang W, Zhang B, Shuai Y, Hong J, Engelgau MM, Li H, Roglic G, Hu Y, Bennett PH. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol 2014; 2:474-80.

[4] Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost effectiveness of strategies for managing people at high risk for diabetes. Ann Intern Med 2005; 143:251–64.

[5] Gilis-Januszewska A, Lindström J, Tuomilehto J, Piwońska-Solska B, Topór-Mądry R, Szybiński Z, Peltonen M, Schwarz PEH, Windak A, Hubalewska-Dydejczyk A. Sustained diabetes risk reduction after real life and primary health care setting implementation of the diabetes in Europe prevention using lifestyle, physical activity and nutritional intervention (DE-PLAN) project. BMC Publ Health 2017; 17:198.

[6] Howells L, Musaddaq B, McKay AJ, Majeed A. Clinical impact of lifestyle interventions for the prevention of diabetes: an overview of systematic reviews. BMJ Open 2016; 6: e013806.

[7] Bo S, Ciccone G, Baldi C, Benini L, Dusio F, Forastiere G, Lucia C, Nuti C, Durazzo M, Cassader M, Gentile L, Pagano G. Effectiveness of a lifestyle intervention on metabolic syndrome. A randomized controlled trial. J Gen Intern Med 2007; 22:1695-1703.

[8] Bo S, Gambino R, Ciccone G, Rosato R, Milanesio N, Villois P, Pagano G, Cassader M, Gentile L, Durazzo M, Cavallo-Perin P. Effects of TCF7L2 polymorphisms on glucose values after a lifestyle intervention. Am J Clin Nutr 2009; 90:1502-8.

[9] Merlotti C, Morabito A, Pontiroli AE. Prevention of type 2 diabetes; a systematic review and meta-analysis of different intervention strategies. Diab Obes Metab 2014; 16:719-27.

[10] Lavie CJ, De Schutter A, Parto P, Jahangir E, Kokkinos P, Ortega FB, Arena R, Milani RV. Obesity and prevalence of cardiovascular diseases and prognosis – the obesity paradox updated. Prog Cardiovasc Dis 2016; 58:537-547.

[11] Oktay AA, Lavie CJ, Kokkinos PF, Parto P, Pandey A, Ventura HO. The interaction of cardiorespiratory fitness with obesity and the obesity paradox in cardiovascular disease. Prog Cardiovasc Dis 2017; 60:30-44.

[12] Kennedy AB, Lavie CJ, Blair SN. Fitness of fatness. Which is more important? JAMA 2018; 319:231-232

[13] Florez H, Temprosa MG, Orchard TJ, Mather KJ, Marcovina SM, Barrett-Connor E, Horton E, Saudek C, Pi-Sunyer XF, Ratner RE, Goldberg RB; Diabetes Prevention Program Research Group. Metabolic syndrome components and their response to lifestyle and metformin interventions are associated with differences in diabetes risk in persons with impaired glucose tolerance. Diab Obes Metab 2014; 16:326-33.

Table 1. Baseline, end of trial, and follow-up variables by arm of the lifestyle intervention (top), and associations between the lifestyle intervention and the outcomes at follow-up (bottom)

	Intervention arm			Control arm			
	Baseline	**End of trial value**	**Follow-up value**	**Baseline**	**End of trial value**	**Follow-up value**	**P [b]**
Number	169	169	148	166	166	138	
Males (%)	41.4	41.4	38.5	42.2	42.2	37.0	0.79
Weight (kg)	81.7±14.9	81.0±15.7	80.0±15.9	81.3±13.5	82.9±14.0	80.7±13.0	0.69
Change [a]			-1.0			+1.0	**0.012**
BMI (kg/m^2)	29.7±4.1	29.4±4.4	29.1±4.3	29.8±4.6	30.4±4.8	30.0±4.8	0.12
Change [a]			-0.43			+0.37	**0.012**
Systolic BP (mmHg)	142.6±14.1	140.7±17.7	138.0±14.9	141.5±15.2	146.3±18.2	143.8±16.5	**0.002**
Change [a]			-5.0			0.0	**0.001**
Diastolic BP (mmHg)	88.2±8.8	85.7±8.9	84.0±8.9	87.8±9.5	87.6±10.6	85.5±9.5	0.17
Change [a]			-4.0			0.0	**0.002**
Glucose (mg/dl)	104.8±14.1	100.2±15.6	98.9±12.0	105.1±12.9	106.4±15.6	104.1±18.3	**0.004**
Change [a]			-4.0			-1.0	**<0.001**

IFG (%)	62.7	42.0	46.0	62.7	56.6	51.5	0.35
Total chol (mg/dl)	225.5±43.7	225.5±41.2	223.9±42.8	233.8±43.2	236.0±43.0	228.4±37.5	0.34
Change [a]			-4.0			+1.0	0.36
HDL chol (mg/dl)	55.2±10.6	55.8±10.4	50.2±11.4	56.1±11.5	53.4±10.2	49.4±11.2	0.56
Change [a]			-3.5			-6.0	**0.033**
Triglycerides (mg/dl)	170.0 (84.0)	145.7 (60.3)	145.0 (56.0)	168.0 (78.0)	157.8 (94.5)	141.5 (89.0)	0.52
Change [a]			-10.5			-1.5	**0.039**

	Intervention arm		**Control arm**		
	Events	**Person-years**	**Events**	**Person-years**	**HR [c]; 95% CI, P**
Diabetes	14	1549	27	1382	0.47; 0.24-0.89, **0.021**
All-cause mortality	21	1613	28	1562	0.71; 0.40-1.26, 0.24
CV mortality	5	1613	11	1562	0.42; 0.15-1.23, 0.11
Incident CV diseases	10	1587	10	1451	0.91; 0.39-2.29, 0.91
Combined CV outcome	12	1587	19	1451	0.60; 0.29-1.24, 0.17

BP=blood pressure; IFG=impaired fasting glucose (fasting glucose ≥100mg/dl and <126 mg/dl); chol=cholesterol; mean±SD or median (interquartile range)

[a] changes =median difference (end-of-follow-up minus baseline values)

[b] between-group difference in the follow-up variables by t-Student test or Mann-Whitney test or chi-square test, as appropriate

[c] HR and 95% CI estimated through a multiple Cox regression model for each condition at follow-up (intervention vs control arm), adjusted for age, sex, and level of education and, for incident CVD and mortality, for smoking habits.