Research Methods

Causal Effects of Intensive Lifestyle and Metformin Interventions on Cardiovascular Disease Risk Factors in Pre-Diabetic People: An Application of G-Estimation

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Abstract

Background: In the presence of non-adherence, intention-to-treat analysis preserves randomization, but does not lead to a valid comparison of outcome between the assigned groups. Using a reanalysis of Diabetes Prevention Program, this study aimed to estimate the causal effect of treatment with intensive lifestyle intervention or metformin *vs*. placebo on blood pressure and lipid profile using G-estimation after accounting for non-adherence.

Methods: The Diabetes Prevention Program randomized 3,052 pre-diabetic individuals to metformin (N = 1015), placebo (N = 1014), or an intensive lifestyle intervention (N = 1023). G-estimation was used to estimate the causal effect of intensive lifestyle intervention or metformin *vs*. placebo on blood pressure and lipid profile in 2,973 patients who had adherence data. For comparison, we also performed the standard intention-to-treat analysis.

Result: The G-estimation results showed that intensive lifestyle substantially improves systolic and diastolic blood pressure and lipid profile. The G-estimates of the effects of metformin *vs*. placebo as well as intensive lifestyle intervention *vs*. metformin on blood pressure and lipid profile were also stronger than the intention-to-treat effect estimates.

Conclusion: G-estimation suggests that intensive lifestyle modification improves known risk factors for cardiovascular disease, including systolic blood pressure, diastolic blood pressure, triglyceride, and HDL levels more than what standard ITT analysis suggests. Adherence to the assigned treatment should be measured in all randomized trials, and G-estimation should be the standard analysis of randomized trials with substantial non-adherence.

Keywords: Cardiovascular disease, G-estimation, intensive lifestyle intervention, metformin, pre-diabetes

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Introduction

The prevalence of type 2 diabetes and pre-diabetes is rapidly increasing worldwide.[1] Pre-diabetes is defined as blood glucose levels above normal but not high enough for a diagnosis of diabetes.[2,3] Pre-diabetes is known as a strong predictor of type 2 diabetes.[4,5] It is estimated that in 2030, approximately 472 million of the world's adult population will have pre-diabetes, and will be therefore, at risk for developing type 2 diabetes, cardiovascular disease, and death even before the development of diabetes.[2,6] In addition, type 2 diabetes shares other common known risk factors with cardiovascular disease such as high blood pressure and abnormal blood lipids. Such risk factors are modifiable, however, and there is a need for strong and valid evidences for supporting related interventions to modify these risk factors. Randomized controlled trial (RCT), as a gold standard design among primary studies, can provide such evidence; nevertheless, RCTs, like other study designs, are subject to several biases.[7] For many reasons such as poor prognosis, participants may not fully adhere to their assigned treatment. In RCTs with non-adherence, intention-to-treat (ITT) analysis, as a primary and standard analysis, preserves randomization, but does not lead to a valid comparison of outcome between the assigned groups. Therefore, in the presence of non-adherence, the estimate of treatment effect could be biased. Specifically, in double-blind placebo-controlled RCTs, this bias underestimates the treatment effect.[8] In RCTs with two active interventions, the direction of this bias will not be predicable.[8,9] There are also conventional approaches to the analysis of RCTs with non-adherence, including per-protocol and as-treated analyses.[10] In per-protocol analysis, only people who adhere to the assigned treatment are included in the analysis. As-treated analysis includes people based on the treatment they receive, regardless of the treatment assignment.[8,10] It is well known that per-protocol and as-treated analyses are prone to selection bias and confounding, respectively and thus, they do not generally yield valid results.[8] Advantages and disadvantages of several methods for the analysis of RCTs with non-adherence have been described elsewhere.[8,11,12] Robins proposed methods to deal with several biases in RCTs and longitudinal studies with time-varying treatment[13–17] and covariates.[18–20] One of these methods is the G-estimation used to correct non-

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adherence. G-estimation is a generalization of instrumental variable analysis and can be used for estimating the causal effect of interventions in RCTs with non-adherence.[14,15]

Certain advices have long been recommended for managing pre-diabetes and type 2 diabetes, including lifestyle modification by increasing exercise and dietary change and initial pharmacotherapy.[21–23] One of the most famous RCT studies in this context is the Diabetes Prevention Program (DPP).[24] Using ITT analysis, the investigators of the DPP demonstrated the effectiveness of intensive lifestyle and metformin interventions compared to placebo in preventing the incidence of type 2 diabetes. They also showed that intensive lifestyle intervention improves cardiovascular disease risk factor status compared with placebo and metformin therapy.[25,26] In DPP, adherence percentages among the participants taking placebo, metformin, and intensive lifestyle intervention were 83%, 73% and 84%, respectively. Therefore, the reported effect estimates using ITT analysis would be biased. Considering the high non-adherence in the DPP, recommendation for routine use of such interventions for all pre-diabetic people should be based on effect estimates accounting for non-adherence. The aim of this paper is re-analysis of DPP data to complement the originally published intention-to-treat effect estimates i.e., estimating the causal effect of continuous treatment with intensive lifestyle intervention or metformin *vs*. placebo on blood pressure and lipid profile using G-estimation.

Methods

DPP trial

The Diabetes Prevention Program (DPP) was a multicenter randomized clinical trial to assess the efficacy and safety of two interventions, namely metformin and intensive lifestyle, in comparison with placebo plus standard lifestyle recommendations on preventing the onset of type 2 diabetes. The secondary outcomes were cardiovascular disease, changes in glycemia, insulin secretion and sensitivity, obesity, physical activity and occurrence of adverse events. For our analysis, we consider systolic blood pressure, diastolic blood pressure and lipid profile (including; Triglycerides, Total cholesterol, high-density lipoprotein (HDL)) as outcomes. Follow-up visits were scheduled at 3-month intervals.[24]

Study population

A total of 3,052 non-diabetic individuals were included, aged at least 25 years with impaired glucose tolerance and fasting plasma glucose values of 95 – 125 mg/dL (5.3 – 6.9 mmol/L) and a body mass index (calculated as weight (kg) divided by height (m) squared) of 24 or higher (22 or higher in Asians) from 27 clinical centers in the US. Women, the elderly, and members of minority groups such as African Americans, Hispanic Americans, Asian and Pacific Island Americans, and Native Americans were over-sampled.

Interventions

Participants were randomly assigned to standard lifestyle recommendations plus metformin (N = 1015) at a dose of 850 mg twice daily, standard lifestyle recommendations plus placebo (N = 1014) twice daily, or an intensive lifestyle intervention (N = 1023) designed to achieve and maintain a weight loss of at least 7% and a level of physical activity of at least 150 minutes per week. Assignments to metformin and placebo were double-blinded.

Statistical analysis

A total of 15 people (0.5%) who died due to any reason were excluded from the analysis. We used pill count data available for the last week of each visit for participants in the metformin and placebo groups, assuming that lack of adherence data is random, and that the pattern of non-adherence for the last week holds for the whole 3-month visit.[27] For the intensive lifestyle intervention group, non-adherence was defined as failure to achieve the goal of at least 150 minutes of physical activity during the last week of each visit. Hypertension was defined as a self-reported diagnosis of hypertension or blood pressure $\geq$ 140/90 mmHg at the baseline visit.

ITT analysis simply compares the mean of outcome variables between groups and was performed using generalized equation estimations (GEE) with exchangeable correlation structure. To account for within-subject correlation, 95% confidence intervals were derived using cluster robust standard error. G-estimation was used to estimate the causal effect of metformin *vs*. placebo, intensive lifestyle intervention *vs*. placebo, and intensive lifestyle intervention *vs*. metformin after accounting for non-adherence. Bias-corrected bootstrap 95% confidence intervals using 1000 resampling of the participants were calculated. See appendix for technical details about the G-estimation. The G-estimation codes are available from: URL: https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book. All analyses were performed using Stata version 14 (Stata Corp, College Station, TX, USA).

Result

Out of 3,052 participants taking metformin, intensive lifestyle intervention or placebo, 2,973 (97.4%) had adherence data. The median (IQR) of follow-up time was 2.74 years. Table 1 presents the baseline characteristics of the study participants with adherence data. Table 2 provides the ITT estimate and G-estimate of the effects of intensive lifestyle intervention or metformin *vs*. placebo on systolic blood pressure and diastolic blood pressure during the study period. In ITT analysis, intensive lifestyle intervention decreased systolic blood pressure and diastolic blood pressure by an average of 2.53 (95%CI: -3.60, -1.47) and 2.03 (95%CI: -2.80, -1.19) mmHg per year, respectively, compared to the placebo group. However, using the G-estimation, for each year of continuous treatment with intensive lifestyle intervention, the mean systolic blood pressure and diastolic blood pressure decreased by 9.37 (95%CI: -14،44, - 5.80) and 7.34 (95%CI: -10.85, - 4.88) mmHg, respectively, compared to placebo. Also, a similar result was observed for intensive lifestyle intervention *vs*. metformin: the G-estimates were stronger than ITT estimates (See Table 2). Table 3 shows a significant reduction in Triglycerides using ITT analysis in favor of intensive lifestyle intervention in comparison to metformin or placebo, while metformin had no significant effect on this outcome compared to placebo. G-estimation suggests a more substantial reduction than the ITT effect for all lipid profile variables. In addition, ITT analysis showed a significant increase in HDL for intensive lifestyle intervention compared to placebo, but for intensive lifestyle intervention *vs*. metformin, this increase was not statistically significant at 5% level. Again, the G-estimates indicate a marked increase in HDL than ITT estimates for all the above-mentioned comparisons.

Table 1. Baseline characteristics of the study participants with adherence data (N = 2973)

Characteristic	ILI† (N = 1010)	Metformin (N = 985)	Placebo (N = 978)
Sex (female)	679 (67.2%)*	647 (65.7%)	662 (67.6%)
Age group			
< 40	164 (16.2%)	127 (12.9 %)	136 (13.9%)
40–44	153 (15.2%)	151(15.3%)	141 (14.4%)
45–49	192 (19.0%)	184 (18.7%)	225 (23.0%)
50–54	146 (14.5%)	206 (20.9%)	156 (16.0%)
55–59	131 (13.0%)	114 (11.6%)	128 (13.1%)
60–64	103 (10.2%)	967 (9.9%)	95 (9.7%)
≥ 65	121 (12.0%)	106 (10.8%)	97 (9.9%)
BMI group			
< 30 kg/m^2	332 (32.9%)	325 (33.0%)	311 (31.8%)
≥ 30 to < 35 kg/m^2	308 (30.5%)	307 (31.2%)	282 (28.8%)
≥ 35 kg/m^2	370 (36.6%)	353 (35.8%)	385 (39.4%)
Race/Ethnicity			
Caucasian	575 (56.9%)	576 (58.5%)	557 (57.0%)
African American	199 (19.7%)	213 (21.6%)	207 (21.2%)
Hispanic, of any race	174 (17.2%)	156 (15.8%)	160 (16.4%)
All other	62 (6.1%)	40 (4.1%)	54 (5.5%)
Hypertension	170 (16.83%)	156 (15.84%)	150 (15.33%)
SBP §	124.1 (14.7%)	124.5 (14.9%)	123.9 (14.5%)
DBP §	78.80 (9.2%)	78.4 (9.5%)	78.2 (9.3%)
Triglyceride ǂ	162.6 (97.1%)	158.8 (90.8%)	166.4 (92.4%)
Cholesterol ǂ	205.1 (36.3%)	203.1 (35.5%)	202.7 (36.1%)
HDL ǂ	46.2 (12.5%)	46.1 (11.5%)	44.8 (11.5%)

†Intensive Lifestyle Intervention; *No.(%) or Mean (SD); §SBP: Systolic blood pressure, DBP diastolic blood pressure (mmHg); ǂ mg/dL.

Table 2. ITT- and G- estimates of the effect of intensive lifestyle intervention or metformin *vs*. placebo per year on blood pressure

		ILI§ *vs.* placebo		Metformin *vs.* placebo		ILI§ *vs.* Metformin	
Outcome variable	**Analysis method**	**β (95% CI) N = 2023**	**β (95% CI) N = 1988ǂ**	**β (95% CI) N = 2027**	**β (95% CI) N = 1963ǂ**	**β (95% CI) N = 2024**	**β (95% CI) N = 1995ǂ**
SBP**	**Intent-to-treat** §	-2.39 (-3.44, -1.35)	-2.53 (-3.60, -1.47)	0.21 (-0.81, 1.24)	0.11 (-0.94, 1.15)	-2.61 (-3.66, -1.55)	-2.64 (-3.71, -1.57)
	G-estimation†	- - -	-9.37 (-14،44, - 5.80)*	- - -	-4.72 (-12.16, 2.09)*	- - -	-7.78 (-12،32, - 4.32)*
DBP**	**Intent-to-treat** §	-1.99 (-3.63, -1.35)	-2.03 (-2.80, -1.19)	-0.02 (-0.66, 0.61)	-0.05 (-0.70, 0.60)	-1.97 (-2.62, -1.33)	-1.99 (-2.64, -1.33)
	G-estimation†	- - -	-7.34 (-10.85, - 4.88)*	- - -	-4.28 (-8.66, -1.66)*	- - -	-5.91 (-9.26, - 3.62)*

§Intensive Lifestyle Intervention; §Using GEE; ǂParticipants with adherence data; †G-estimation using grid search; *Bias-corrected bootstrap 95% CI; **SBP: Systolic blood pressure, **DBP diastolic blood pressure (mmHg).

Table 3. ITT- and G- estimates of the effect of intensive lifestyle intervention or metformin *vs*. placebo per year on lipid profile

		ILI§ *vs.* placebo		Metformin *vs.* placebo		ILI§ *vs.* Metformin	
Outcome variable	**Analysis method**	**β (95% CI) N = 2023**	**β (95% CI) N = 1988ǂ**	**β (95% CI) N = 2027**	**β (95% CI) N = 1963ǂ**	**β (95% CI) N = 2024**	**β (95% CI) N = 1995ǂ**
Triglyceride	**Intent-to-treat** §	-15.74 (-22.60, -8.90)	-15.60 (-22.55, - 8.66)	-5.80 (-12.80, 1.17)	-5.11 (-12.30, 2.04)	-9.88 (-16.60, - 3.16)	-10.48 (-17.31, - 3.70)
	G-estimation†	- - -	-66.35 (-114.54, - 18.15)*	- - -	-23.14 (-60.80, 2.57)*	- - -	-43.55 (-69.72, - 20.90)*
Cholesterol	**Intent-to-treat** §	-2.19 (-4.94 , 0.56)	-1.52 (-4.30, 1.26)	-1.31 (-3.98, 1.37)	-0.92 (-3.63, 1.80)	-0.87 (-3.58, 1.83)	-0.61 (-3.34, 2.13)
	G-estimation†	- - -	-10.95 (-14،03, 0.68)*	- - -	-9.61 (-12.35, 8.83)*	- - -	-1.76 (-4،44, 0.57)*
HDL	**Intent-to-treat** §	2.02 (1.05, 2.99)	2.05 (1.06, 3.03)	1.67 (0.74, 2.60)	1.67 (0.71, 2.63)	0.35 (-0.64, 1.34)	0.37 (-0.63, 1.39)
	G-estimation†	- - -	13.60 (6،08, 17.88)*	- - -	11.51 (7.12, 23.76)*	- - -	1.09 (-0،43, 1.75)*

§Intensive Lifestyle Intervention; §Using GEE; ǂParticipants with adherence data; †G-estimation using grid search; *Bias-corrected bootstrap 95% CI.

Discussion

Using G-estimation, we estimated the effect of continuous treatment with intensive lifestyle intervention or metformin compared to placebo on blood pressure and lipid profile in a randomized trial with substantial non-adherence. In presence of non-adherence, ITT analysis underestimates the effect of intervention in placebo-controlled RCTs, but it may not be conservative in trials with two active treatments (e.g., intensive lifestyle intervention *vs.* metformin comparison).[9] Thus, recommendations based on the results of ITT analysis may be inaccurate. Per-protocol and as-treated analysis are frequently used as naïve alternatives to analyze RCTs with non-adherence,[28] but it is well-known that using these alternative approaches are subject to confounding or selection bias and they generally yield biased effect estimates.[7,29–31] The effect of interest is per-protocol effect i.e., the effect that would have been observed if all patients in the trial had adhered to the study protocol.[7] This effect may be more interesting for patients, clinicians and health care providers. Similar to ITT analysis, complete follow-up is needed for G-estimation; in the presence of censoring (loss to follow-up or competing risks), it is necessary to use other methods like inverse probability weighting to adjust for selection bias induced by censoring.[18,32]

In the DPP data, the effects of G-estimates were stronger than the ITT effect estimates for all outcome variables. The results of this study show that continuous treatment with intensive lifestyle substantially improves systolic and diastolic blood pressure and lipid profile and thus, it may have clinical application in reducing cardiovascular disease risk for pre-diabetic people. This can be clearly seen for blood pressure where the G-estimate, but not the ITT estimate, of the healthy lifestyle intervention is clinically important.[33,34] However, both ITT and G-estimation yielded similar results regarding the rejection of null hypothesis of no effect (i.e., 95% confidence interval does not include the value of zero). The G-estimates of the effects of metformin *vs.* placebo as well as intensive lifestyle intervention *vs.* metformin on blood pressure and lipid profile were also stronger than the ITT estimates.

In this study, last week pill count data at each visit were used for the whole 3-month visit. In other words, missing data on non-adherence given at each visit was assumed to be at random. Cnaan, et al. showed that past week information of adherence is a good proxy for recall adherence to treatment in the last six months.[27] This self-reported pill count in the last week of each visit is an important limitation of our G-estimation analysis. To fully account for non-adherence using G-estimation, the adherence data for the whole follow-up time is needed.

In our analysis, we conducted the randomization type of G-estimation which only relies on baseline randomization and correct specification of the structural model (see appendix). With time-varying covariates repeatedly measured during follow-up, one can use the observational version of G-estimation as well as other causal methods including inverse-probability-of-treatment weighting.[18,35]

In conclusion, G-estimation suggests that intensive lifestyle modification improves known risk factors for cardiovascular disease, including systolic blood pressure, diastolic blood pressure, triglyceride, and HDL levels, much more than what standard ITT analysis suggests. We recommend that adherence to the assigned treatment should be measured in all RCTs, and for RCTs with non-negligible non-adherence, the analysis should include G-estimation along with ITT.

Conflict of interest

The authors have no conflicts of interest to declare for this study.

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Appendix

Let the random variable R (For example; 1: intensive lifestyle intervention group, 0: placebo group) and Y denote intervention assignment and systolic blood pressure, respectively. Let $d(a)_t$ denote indicators of the received intervention at day t (i.e., 1: yes, 0: no). We use $\bar{A}(t)$ and $\bar{a}(t)$ to denote the intervention history and its realization through time t, respectively. Let $Y^{\bar{a}}$ be the counterfactual outcome under intervention $\bar{a}$ e.g., continuous treatment with intensive lifestyle intervention is $\bar{1}$= {1,1,1,..} and never treatment with intensive lifestyle intervention is $\bar{0}$ ={0,0,0,..}. We used a structural mean model (SMM) of the form:[14]

$$Y^{\bar{0}} = Y^{\bar{a}} - \omega \sum_{t=o}^{T} d(\mathrm{a})_t \quad (1)$$

Where $\sum_{t=o}^{T} d(\mathrm{a})_t$ is the duration of the received intervention from baseline to the end of study at day t=T (In our example T=2.99 year). The parameter ω is measures of the increase (or decrease) in the mean outcome per each additional time period (year in our study) on received intervention. By consistency assumption (i.e., $Y^{\bar{a}} = Y$),[9] model (1) implies:

$$Y^{\bar{0}} = Y - \omega \sum_{t=o}^{T} d(\mathrm{A})_t \quad (2)$$

Model (2) relates a participant's observed outcome and observed intervention history to her/his counterfactual time if there were no adherence to intervention. As neither $Y^{\bar{0}}$ nor ω is known in model (2), we present SMM as

$$H(p) = Y - \omega \sum_{t=o}^{T} d(\mathrm{A})_t \quad (3)$$

Where p can take any value and H(p) = $Y^{\bar{0}}$ if p=ω. As randomization implies, independence between the intervention assignment R and the counterfactual outcome Y^0, the G-estimate $\hat{\omega}$ of the parameter ω is the value of p that makes $\hat{\beta}_1 = 0$ (*P*-value = 1) in the following logistic regression model

$$logitPr\left[\mathrm{R} = 1 \middle| Y^{\bar{0}}\right] = \beta_0 + \beta_1 Y^{\bar{0}} \quad (4)$$

The test-based 95% confidence interval for $\hat{\omega}$ includes all the values of ω that produce values of $\hat{\beta}_1$ with P-values over 0.05. Estimation can be obtained by a fine grid search over the specified range for ω. In addition to the test-based 95% CI, bootstrap 95% CI can be calculated.

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