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Metformin Treatment With or Without Mediterranean Diet for the Prevention of Age-Related Diseases in People With Metabolic Syndrome: The MeMeMe Randomized Trial

Patrizia Pasanisi, Andreina Oliverio, Ivan Baldassari, Eleonora Bruno, Elisabetta Venturelli, Manuela Bellegotti, Giuliana Gargano, Daniele Morelli, Antonio Bognanni, Marta Rigoni, Paola Muti, and Franco Berrino

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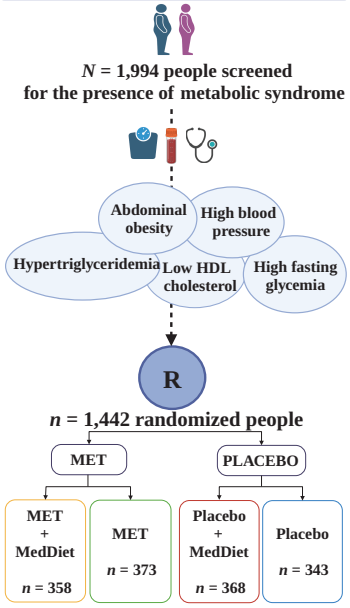
OBJECTIVE: The Metformin and Dietary Restriction to Prevent Age-Related Morbid Events in People With Syndrome (MeMeMe) randomized trial tested whether 1,700 mg/day metformin (MET) with or without an intervention of a Mediterranean diet (MedDiet) reduces the cumulative incidence of the major noncommunicable diseases (NCDs) in people with metabolic syndrome.

METHODS

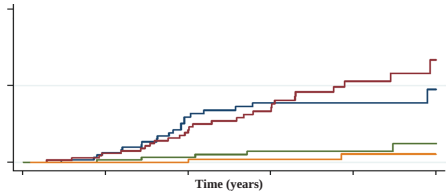


RESULTS

Cumulative Hazard of NCDs

Hazard ratio (HR) (95% CI) Adjusted			
Placebo	Placebo+MedDiet	MET	MET+MedDiet
1	1.09 (0.70-1.70)	**0.51 (0.30-0.86)**	**0.48 (0.29-0.82)**

Cumulative Hazard of Type 2 Diabetes



Placebo	343	300	232	189	109	43
Placebo+MedDiet	368	330	269	213	130	46
MET	373	319	271	223	142	43
MET+MedDiet	358	316	274	220	130	38

HR (95% CI) Adjusted			
Placebo	Placebo+MedDiet	MET	MET+MedDiet
1	1.23 (0.67-2.24)	**0.20 (0.10-0.55)**	**0.08 (0.02-0.35)**

CONCLUSIONS: 1,700 mg/day MET is effective in the prevention of diabetes, but not other NCDs, in people selected on the basis of metabolic syndrome.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  We hypothesized that metformin may affect noncommunicable diseases in people with metabolic syndrome.
- **What is the specific question we wanted to answer?**
  The Metformin and Dietary Restriction to Prevent Age-Related Morbid Events in People With Metabolic Syndrome (MeMeMe) trial was designed to test whether 1,700 mg/day metformin with or without a Mediterranean dietary intervention reduce the cumulative incidence of major noncommunicable diseases in people with metabolic syndrome.
- **What did we find?**
  Metformin reduced the cumulative incidence of age-related diseases. This effect was explained by the prevention of type 2 diabetes, with 48 cases in the placebo groups versus 7 in the metformin groups.
- **What are the implications of our findings?**
  We strongly demonstrated that metformin is effective in preventing diabetes.

Metformin Treatment With or Without Mediterranean Diet for the Prevention of Age-Related Diseases in People With Metabolic Syndrome: The MeMeMe Randomized Trial

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OBJECTIVE

The Metformin and Dietary Restriction to Prevent Age-Related Morbid Events in People With Metabolic Syndrome (MeMeMe) trial tested whether 1,700 mg/day metformin (MET) with or without a Mediterranean diet (MedDiet) intervention could reduce the cumulative incidence of major noncommunicable diseases in people with metabolic syndrome.

RESEARCH DESIGN AND METHODS

A total of 1,442 participants were randomly assigned to one of four interventions: *1*) MET (1,700 mg/day) plus MedDiet intervention (MET+MedDiet); *2*) placebo plus MedDiet intervention; *3*) MET (1,700 mg/day) alone; and *4*) placebo alone. Participants were followed up for 3 years on average. The primary outcome was the cumulative incidence of major noncommunicable diseases (including type 2 diabetes, cardiovascular diseases, and cancer). Secondary outcomes were the incidence of type 2 diabetes and the changing prevalence of metabolic syndrome.

RESULTS

The crude incidence of the major noncommunicable diseases was 6.7 cases per 100 person-years in the MET+MedDiet group, 6.9 in the MET alone group, 13.3 in the placebo plus MedDiet group, and 11.3 in the placebo group. The differences were fully explained by the reduction of type 2 diabetes, which was 80% and 92% lower in the MET and MET+MedDiet groups, respectively, compared with placebo.

CONCLUSIONS

The use of 1,700 mg/day MET is effective to prevent diabetes in people selected on the basis of metabolic syndrome.

Noncommunicable diseases (NCDs) account for almost 90% of deaths in the European region (1). A major risk factor for the development of NCDs is metabolic syndrome (MetS), a clinical condition defined as a clustering of metabolic risk factors such as abdominal obesity, high blood pressure, dyslipidemia, and high fasting

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glycemia (2). MetS is responsible for a fivefold increased risk of type 2 diabetes, 2.5-fold increased cardiovascular mortality, twofold higher risk of coronary and cerebrovascular diseases, and 1.5-fold increase in the risk of all-cause mortality (3,4). MetS also increases the risk of several common cancers, including colorectal and breast (postmenopausal) cancer (5).

The Mediterranean diet (MedDiet), largely based on unrefined cereal products, pulses, vegetables, olive oil, nuts, fruit, moderate wine, occasionally fish and cheese, and rarely other animal products, has been proven to affect MetS (6). Higher adherence to the MedDiet is associated with reduction of cardiometabolic risk factors and lower prevalence of MetS, and studies show that MedDiet interventions can revert MetS (7–9).

Metformin (MET) is a calorie-restriction mimetic drug widely used as first-line therapy for type 2 diabetes (10). Recently, many additional properties of MET emerged, with evidence demonstrating its potential protective effect on multiple disorders (11,12). Metformin improves the prognosis of liver diseases and polycystic ovary syndrome (13,14) and exerts a preventive effect on renal diseases and obesity (15,16). Despite a high statistical heterogeneity in studies, a recent meta-analysis found that people with diabetes receiving MET treatment had a decreased risk of developing cancer (17). Data on the potential protective effect of MET in people with cancer are controversial (18). Studies of individuals without diabetes are needed to better understand the role of MET in the prevention of NCDs.

In this context, we designed and conducted the Metformin and Dietary Restriction to Prevent Age-Related Morbid Events in People With Metabolic Syndrome (MeMeMe) trial, a randomized controlled trial involving volunteers at high age-related risk of NCDs (50-79 years old) and the presence of MetS (19–22). The study was designed to investigate whether a treatment of 1,700 mg/day MET with or without a MedDiet intervention can reduce the cumulative incidence of major NCDs, such as type 2 diabetes, cardiovascular diseases, and cancer.

RESEARCH DESIGN AND METHODS

The MeMeMe trial (EudraCT no. 2012–005427-32; ClinicalTrials.gov identifier NCT02960711) was supported by the European Research Council (grant 322752) and approved by the institutional review board and ethical committee of the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano (approval no. INT 85/13). The study was planned to last 5 years (with an extension of 1 year according to a European Research Council amendment), including the enrollment period, up to 4 years, and follow-up. The study was conducted in full conformance with the principles of the Declaration of Helsinki. The MeMeMe trial had a single enrollment center at the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano. All participants were fully informed about the study and signed a written informed consent before any trial-specific procedure or treatment.

Study Design

Detailed information about the study have been reported previously (19–22). Briefly, the MeMeMe trial had a 2 × 2 factorial design with 1,600 volunteers with MetS to be randomly allocated in four arms of 400 each: *1*) MET (1,700 mg/day) plus MedDiet (MET+MedDiet) intervention; *2*) placebo plus MedDiet intervention; *3*) MET (1,700 mg/day) alone; and *4*) placebo alone.

MetS was defined on the basis of the presence of at least three components out of five, according to the thresholds proposed by the International Diabetes Federation (2): blood pressure ≥130/85 mmHg, fasting plasma glucose ≥100 mg/dL, triglycerides ≥150 mg/dL, HDL <50 mg/dL for women and <40 mg/dL for men, or treatment of these conditions—except for waist circumference, for which we used the threshold of ≥100 cm in men instead of >94 cm, and ≥85 cm in women instead of >80 cm (23).

Study Participants

Eligible study participants were people aged 50–79 years. They all received, at baseline, the World Cancer Research Fund general recommendations of healthy diet and were required to complete a personal data form; complete a form including medical history and behavioral factors; provide a fasting 20-mL blood sample and attend a clinical and anthropometric visit for screening presence of MetS; provide information on their health status, and to permit the trial investigators to contact their general practitioners, consult clinical notes and examine biopsy material, as necessary; and complete a 24-hour food frequency diary of the previous day intake at baseline, at the end of the first year, and annually for the duration of the study.

Exclusion criteria included people without MetS; with a previous diagnosis of diabetes or fasting glycemia ≥126 mg/dL (7.0 mmol/L) in two consecutive blood samples, or taking glucose-lowering medication; with serum creatinine >124 μL/L; or with a previous diagnosis of cardiac or hepatic insufficiency or cancer (in the past 5 years).

People with MetS started the training period with 500 mg/day MET. Annual clinical visits and blood metabolic examinations were repeated for the duration of the study. All participants were actively followed up from the start of the intervention, set as the date of randomization, for a maximum of 5 years.

Procedures

Randomization

The MeMeMe trial comprised two distinct randomizations: MedDiet intervention assignment (based on participants' registration data) and MET or placebo assignment (after the screening examinations and MET training period). The first randomization (assignment to the MedDiet intervention) was stratified according to sex, but members of the same family were included in the same randomization group (cluster randomization). The second randomization (assignment to MET or placebo) was conversely individual, double-blinded, and stratified according to sex and age (<67 and ≥67 years) (20).

MET Treatment

The participants with MetS were treated with an initial low dose of MET: 500 mg taken orally once a day for 1 month. Participants who experienced distressing side effects were not included in the study. Volunteers who passed this training period were then randomized to either the placebo group or the MET group. After randomization, the dose of MET was increased to 850 mg once a day for two more months; placebo tablets also were given once a day. The full treatment

of 850 mg of MET twice a day, with placebo tablets also given twice a day, was then started. The adherence to the treatment was assessed on the basis of the MeMeMe trial allocation register with all the dates for deliveries to each participant (20).

Dietary Intervention

The dietary intervention was aimed to result in a comprehensive qualitative dietary change, based on the traditional Italian Mediterranean diet. Participants did not receive a specific dietary plan with calorie count but did receive dietary recommendations. To control body weight and improve metabolic parameters, volunteers randomized to the MedDiet groups were encouraged to:

- include highly satiating foods such as whole grains, legumes, and high-fiber vegetables as major components of their diet;
- reduce high glycemic/insulinemic index foods, such as refined products, potatoes, sugar, and milk;
- reduce foods rich in saturated fats (e.g., red and processed meats), and fatty dairy products, and to avoid sources of trans fatty acids (e.g., margarines).

Volunteers in the MedDiet groups were invited to participate in monthly dietary activities during the first year (e.g., thematic kitchen courses, community meals, nutritional conferences). Other nutritional activities were scheduled every 3 months in the second year and at 4-month intervals afterward. To guarantee compliance with the drug administration and annual examinations, people randomized in the MET or placebo alone groups were invited to four community meals during the first year of the study.

Dietary Assessment

The 24-h food frequency diary used for dietary assessment contains a list of 38 foods or food-group items (usually consumed in Italy), without any information on portion size, weight, or recipe. Volunteers had to indicate whether, on the previous day, they had eaten or not eaten the specified food or from the food group at breakfast, lunch, dinner, and breaks. For each dietary item, therefore, we counted the number of times it was consumed per day (i.e., the frequency).

For the analysis, an a priori classification of recommended and discouraged foods was created based on the foods we aimed to promote or reduce in consumption. Recommended foods were whole-grain products (whole bread, whole rice, other whole grain cereals, unsweetened flakes); vegetables (except potatoes); legumes; fish; and nuts and seeds. Discouraged foods were sugary beverages; alcoholic drinks; sweets; sugar and added sugars; white rice; potatoes; traditional dishes rich in cheeses and meat; red meat and processed meat; and butter and other discouraged seasonings (butter, lard cream, margarine, ready sauces, mayonnaise, ketchup). Pasta, milk, fruit, white meat, and eggs were considered neutral foods.

On the basis of this classification, we built an indicator of compliance, the Dietary Index, by adding one point for every frequency of recommended foods and subtracting one point for every frequency of discouraged foods consumed in the day (24).

Laboratory Analysis

Fasting blood samples were promptly centrifuged and analyzed after collection. We measured plasma levels of glucose, triglycerides, and total, HDL, and LDL cholesterol by routine biomedical techniques. The personnel who analyzed the samples were blinded about the participants' randomization group.

Outcome Measurements

The primary outcome was the cumulative incidence of major NCDs, including type 2 diabetes, cardiovascular diseases, and cancer. Secondary outcomes were the incidence of type 2 diabetes and the changing prevalence of MetS and its metabolic and anthropometric components. Participants were actively contacted for the duration of the study and copies of all relevant clinical records were obtained to confirm any outcome diagnosis.

Cancer cases were registered according to the rules and definitions of the European Network of Cancer Registries (25). For the definition of diabetes, according to the 1997 criteria of the American Diabetes Association (26), a fasting plasma glucose level $\geq$126 mg/dL (7.0 mmol/L) in two consecutive tests (within 2 months) was considered. Most diabetes cases were detected at the annual follow-up. Few cases were detected independently from the study, and the clinical diagnosis was checked.

People with suspected coronary heart disease or cerebrovascular disease were identified on hospital discharge forms with ICD9-CM 410-414 codes or procedure codes for coronary revascularization, and, respectively, with codes 342, 430-434, 436-438 or procedure codes for carotid revascularization. Clinical records were retrieved to verify the diagnoses. Ischemic thrombotic stroke was diagnosed when brain infarction was mentioned in the diagnosis and/or confirmed on the basis of imaging. Hemorrhagic stroke was diagnosed when cerebral hemorrhage was mentioned in the diagnosis or confirmed by imaging. Cause of death was also registered.

Statistical Analysis

We originally estimated a 94% statistical power to detect a significant 33% decrease in total NCD incidence, considering 1,600 randomized participants. With 1,442 volunteers properly randomized, the actual power of the study is 87%.

The characteristics of the study population were summarized by randomization group using frequencies or means and SD, as appropriate. Body mass index was defined as body weight (in kilograms) divided by height (in meters) squared. Waist-to-height ratio (WtHR) was defined as the ratio of waist circumference to height (both measured in centimeters). We analyzed the magnitude of changes in anthropometric, metabolic, and dietary variables by using the difference between the 1-year and the baseline measurements for each participant in the four groups.

The main analysis followed the intention-to-treat principle. The statistical analysis focused on the incidence of total events (type 2 diabetes, cancer, and major cardiovascular diseases). The analysis was repeated excluding the cancer cases that occurred in the first year. Further analyses were focused on type 2 diabetes incidence. Sensitivity analyses were performed in which participants were stratified by impaired baseline fasting glucose level and included only the first family member enrolled into the trial.

The effect of interventions was assessed by hazard ratios (HRs) and 95% CIs, using the Cox proportional hazards model. The proportionality of hazards was checked (Schoenfeld test) for both NCDs and type 2 diabetes incidence. Product terms between randomization assignment and indicator variables for covariate categories were included in Cox regression models. Interactions between randomization group and each covariate were formally tested for significance with likelihood ratio tests. The results are presented as HRs and 95% CIs.

A P value <0.05 was taken as significant. All statistical tests were two-sided. Analyses were done using the STATA 16 statistical package (StataCorp, College Station, TX).

RESULTS

From 2013 to 2018, of the 1,994 potentially eligible volunteers who participated in the baseline screening examinations, 1,442 participants with MetS (mean age ± SD, 62.5 ± 6.8 years) were randomly assigned to one of the four interventions: 358 to MET+MedDiet intervention, 373 to MET alone, 368 to placebo + MedDiet intervention, and 343 to placebo alone (Fig. 1). Among the MetS components, low HDL cholesterol (97%), high blood pressure (96%), and large waist circumference (90%) were the most represented, followed by hyperglycemia (56%) and hypertriglyceridemia (28%).

After the randomization, ∼2% of participants left the trial due to MET intolerance, and ∼5% continued with half a dose of MET or placebo. On average, MeMeMe participants received ∼1,400 mg/day MET or placebo in each randomized group. Approximately 30% of participants in each group did not get the full dose of treatment.

The MeMeMe volunteers were followed up for 3.0 years, on average. Nine deaths occurred during the trial (Fig. 1), six after a major event (cancer) and three due to other causes (n = 1 car accident, n = 2 for infectious disease). The general characteristics of the MeMeMe population are reported in Table 1.

After 1 year of intervention (Table 2), the MET alone and MET+MedDiet groups had significantly reduced body weight, BMI, waist circumference, WtHR, and glycemia compared with the placebo group. Additionally, MET+MedDiet group had significantly reduced total and LDL cholesterol levels compared with the placebo group. Compared with the placebo + MedDiet group, the MET-alone and MET+MedDiet groups significantly improved body weight, BMI, and glycemia; the MET+MedDiet group also had significantly reduced waist circumference and total and LDL cholesterol levels. Despite the MET+MedDiet group globally experiencing the major improvements, no significant difference was observed compared with the MET-alone group.

Similar results were observed when comparing MET versus placebo, controlling for the MedDiet intervention (Supplementary Table 1); however, significant changes in waist circumference and WtHR were found when comparing the MedDiet versus no MedDiet intervention, controlling for MET or placebo (Supplementary Table 1).

The changes in consumption of recommended (increase) and discouraged foods (decrease) were minor and fairly homogenous. Overall, we did not observe any significant difference among groups in the change of food frequency consumption in the first year (Table 2) of during the 5 years of follow-up (Supplementary Fig. 1).

The prevalence of MetS components was reduced during the 5-year follow-up in all the randomized groups, with the exception of blood pressure and HDL cholesterol (Supplementary Fig. 2). The percentage of participants with MetS significantly differed between the MET and placebo groups only in the first year after randomization ($P < 0.01$), even if the cohort continued to maintain distance between the MET and placebo groups during the 5 years of the trial (Supplementary Fig. 3).

In the first 2 years of the study, MET significantly reduced glycemia in both participants with and those without impaired fasting glucose levels (Supplementary Table 2).

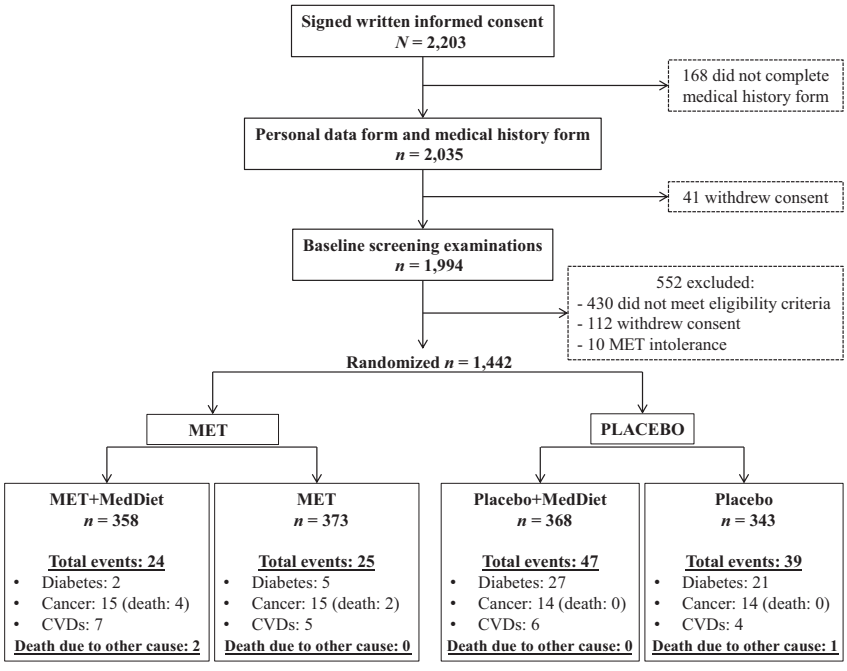


Figure 1—Flowchart of the study.

Intention-to-Treat Analysis

The distribution of NCDs according to randomization group is reported in Fig. 1. We did not observe any difference in the incidence of cardiovascular diseases or cancer in the four randomized groups. Cancer mortality was confined to the MET-treated groups (n = 6 deaths compared with 0 in the placebo groups). These deaths resulted from a lung cancer after 6 months of treatment (received four of the half-dose treatments), a bowel cancer after 10 months of inconstant treatment (received a fourth of the prescribed dose), a multiple myeloma after 12 months of half-dose treatment, a pancreatic cancer after 18 months of full-dose treatment, a malignant melanoma after 30 months of

Table 1—Baseline characteristics of the MeMeMe population

Characteristic	Placebo (n = 343)	Placebo + MedDiet (n = 368)	MET (n = 373)	MET + MedDiet (n = 358)
Age, mean ± SD (years)	62.8 ± 6.7	62.0 ± 6.8	62.6 ± 6.9	62.7 ± 6.7
Sex (%)				
Female	63.0	65.0	64.3	68.2
Male	37.0	35.0	35.7	31.8
Marital status (%)				
Unmarried	14.9	16.4	17.5	17.1
Married	68.5	68.8	66.9	65.2
Divorced	12.5	9.0	10.8	9.0
Widowed	4.1	5.8	4.8	8.7
Education (%)				
Primary school	18.2	17.9	17.2	20.7
High school	54.3	53.5	48.7	51.0
Degree and more	27.5	28.6	34.1	28.3
Smoking status (%)				
Never	40.4	44.0	49.3	43.1
Former	49.1	44.6	38.8	47.6
Current smoker	10.5	11.4	11.9	9.3
Cholesterol therapy (% yes)	28.3	24.7	30.3	25.7
Triglyceride therapy (% yes)	4.1	5.2	4.3	5.0
Blood pressure therapy (% yes)	51.9	58.2	52.8	52.8
Body weight, mean ± SD, kg	84.8 ± 16.5	85.8 ± 17.3	83.6 ± 13.7	84.9 ± 16.2
BMI, mean ± SD, kg/m^2	31.3 ± 5.0	31.9 ± 5.3	31.2 ± 4.5	31.6 ± 4.9
Waist circumference, mean ± SD, cm	99.6 ± 12.3	100.4 ± 12.8	98.6 ± 10.9	99.6 ± 11.8
WtHR, mean ± SD	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
Diastolic blood pressure, mean ± SD, mmHg	89 ± 10	89 ± 11	89 ± 9	89 ± 10
Systolic blood pressure, mean ± SD, mmHg	148 ± 19	148 ± 20	146 ± 18	147 ± 19
Fasting glycemia, mean ± SD, mg/dL	102 ± 10	102 ± 10	101 ± 10	100 ± 9
Fasting total cholesterol, mean ± SD, mg/dL	213 ± 37	212 ± 35	216 ± 36	215 ± 39
Fasting HDL cholesterol, mean ± SD, mg/dL	56 ± 14	54 ± 14	58 ± 15	57 ± 14
Fasting LDL cholesterol, mean ± SD, mg/dL	133 ± 34	132 ± 31	134 ± 32	134 ± 34
Fasting triglycerides, mean ± SD, mg/dL	125 ± 53	129 ± 62	119 ± 52	125 ± 70
Dietary Index (RFC-DFC)/day, mean ± SD	−0.7 ± 3.3	−0.7 ± 3.1	−0.5 ± 3.2	−0.8 ± 2.9

DFC, frequency of discouraged food; RFC, frequency of recommended food.

full-dose treatment, and a metastatic cancer probably arising in the gastrointestinal tract after 18 months of full-dose and 24 months of half-dose treatment.

The cumulative incidence of all NCDs (diabetes, cardiovascular diseases, and cancer) was significantly lower in the MET+MedDiet and MET groups than in the placebo + MedDiet and placebo groups. The crude incidence was, respectively, 6.7, 6.9, 13.3, and 11.3 cases per 100 person-years.

Compared with placebo, the adjusted HRs of NCDs were 1.09 (95% CI, 0.70–1.70) in the placebo + MedDiet, 0.51 in the MET group (95% CI, 0.30–0.86), and 0.48 (95% CI, 0.29–0.82) in the MET+MedDiet group. None of these results were affected by adjustment for age (quintiles), baseline BMI (quintiles), and sex. Excluding the 17 cancer cases that occurred in the first year of the study (n = 8 in the MET group, n = 9 in the placebo group), the results did not substantially change.

Figure 2 reports the cumulative hazard curves of type 2 diabetes for all the randomized groups. The incidence of type 2 diabetes was 80% lower in the MET group (HR 0.20; 95% CI, 0.10–0.55) and 92% lower (HR 0.08; 95% CI, 0.02–0.35) in the MET+MedDiet group than in the placebo. These results were not affected by the adjustments for age (quintiles), baseline BMI (quintiles), and sex.

When stratifying the volunteers by impaired plasma glucose at baseline (<110 mg/dL and ≥110 mg/dL), the resulting HRs of diabetes were 0.16 (95% CI, 0.04–0.71) and 0.17 (95% CI, 0.07–0.41), respectively.

The MeMeMe trial included 73 families of two members randomized in the same MedDiet group. Considering only the first member enrolled, the HRs of diabetes were 1.18 (95% CI, 0.67–2.10) in the placebo + MedDiet, 0.21 in the MET group (95% CI, 0.08–0.55), and 0.08 (95% CI, 0.02–0.36) in the MET+MedDiet group.

CONCLUSIONS

Our findings showed that a treatment of 1,700 mg/day MET, with or without a MedDiet intervention, is effective to reduce the cumulative incidence of age-related NCDs in people with MetS. This effect, however, is fully explained by the prevention of type 2 diabetes, with 48 cases in the placebo and placebo + MedDiet groups together versus 7 in the MET and MET+MedDiet groups. Compared with placebo, we observed dramatic 80% and 90% reductions of type 2 diabetes in the MET and MET+MedDiet groups, respectively. We did not observe any effect on the incidence of cardiovascular events or on the incidence of cancer. The unexpected excess in cancer deaths in the MET groups (n = 6 cases versus 0 in the placebo groups) is likely due

Table 2—Intention-to-treat analysis by randomization group

Parameter (change in)	Placebo (n = 287)	Placebo + MedDiet (n = 314)	MET (n = 309)	MET + MedDiet (n = 302)
Body weight (kg)	−1.4 ± 3.9	−1.6 ± 3.6	−2.7 ± 3.8*†	−3.4 ± 5.4*†
BMI (kg/m^2)	−0.5 ± 1.5	−0.6 ± 1.3	−1.0 ± 1.4*†	−1.3 ± 2.0*†
Waist circumference (cm)	0.2 ± 6.0	−0.4 ± 5.4	−1.3 ± 5.3*	−2.1 ± 5.8*†
WtHR	0.001 ± 0.03	−0.002 ± 0.03	−0.01 ± 0.03*	−0.01 ± 0.04*
Diastolic blood pressure (mmHg)	−2.0 ± 9.2	−1.5 ± 9.2	−1.8 ± 8.9	−2.7 ± 8.7
Systolic blood pressure (mmHg)	−1.3 ± 16.4	−0.6 ± 16.8	−1.9 ± 16.4	−2.5 ± 15.5
Glycemia (mg/dL)	0.1 ± 8.4	−0.3 ± 8.7	−2.8 ± 8.8*†	−2.8 ± 8.0*†
Total cholesterol (mg/dL)	−6.6 ± 28.9	−6.0 ± 28.4	−8.0 ± 25.2	−12.3 ± 31.0*†
HDL cholesterol (mg/dL)	0.4 ± 6.9	0.5 ± 7.6	1.0 ± 7.3	1.3 ± 7.5
LDL cholesterol (mg/dL)	−6.3 ± 25.8	−4.7 ± 26.0	−8.8 ± 21.2	−12.2 ± 28.5*†
Triglycerides (mg/dL)	0.8 ± 45.5	−6.0 ± 54.2	−1.8 ± 44.2	−5.5 ± 58.5
RFC (frequency/day)	0.4 ± 2.4	0.3 ± 2.4	−0.2 ± 2.7	0.1 ± 2.7*
DFC (frequency/day)	−1.3 ± 2.8	−1.3 ± 2.7	−1.3 ± 2.5	−1.4 ± 2.5
DI (RFC-DFC)/day	1.6 ± 3.8	1.6 ± 3.4	1.1 ± 3.5	1.5 ± 3.4

Data are presented as mean ± SD of differences between 1-year and baseline. ANOVA (Bonferroni correction) controlling for sex, age (quintiles), baseline BMI (quintiles), and the baseline value of the parameter under study was used. DFC, frequency of discouraged food; RFC, frequency of recommended food. *$P < 0.05$ for the comparison with placebo. †$P < 0.05$ for the comparison with placebo + MedDiet.

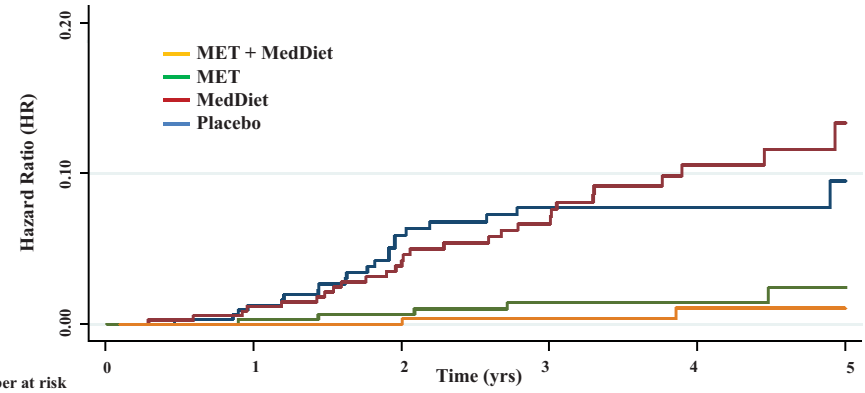
to chance because it involved six different types of cancer, and most of these volunteers received only a fraction of the full MET dose. However, this finding warrants further investigation.

Several trials have demonstrated the effectiveness of MET treatment in the prevention of type 2 diabetes. The Diabetes Prevention Program (DPP) for participants with high-normal levels of fasting plasma glucose (or impaired glucose tolerance) provided evidence to support the concept of diabetes prevention with MET and lifestyle in the early 2000s (27). With the same dose of MET as in the MeMeMe trial, the DPP trial reported reduced incidence of diabetes by 31%, and a significant long-term reduction that persisted after 21 years of follow-up (28). Compared with DPP, our study resulted in a substantially smaller reduction in glycemia after the first year of treatment (approximately −2.8 mg/dL in the MET groups on average vs. −5 mg/dL in DPP). However, contrary to the DPP, in which glycemia returned at baseline levels after 2 years of intervention, the MeMeMe participants continued to reduce their plasma glucose during the 5 years of the study.

Other trials demonstrated a preventive effect of MET treatment in people with impaired fasting glucose, including the Indian Diabetes Prevention Program (29), the Canadian Normoglycemia Outcomes Evaluation (CANOE) study (30), and a study in Pakistan (31). In the MeMeMe trial, only 18.9% of volunteers had a baseline fasting plasma glucose ≥110 mg/dL. Confining the analysis to these cases, the relative risk of diabetes comparing MET versus placebo was about the same as in participants with plasma glucose <110 mg/dL.

To our knowledge, this trial is the first to demonstrate the preventive effect of MET against type 2 diabetes in people selected only on the basis of MetS. Type 2 diabetes affects ∼135 million people aged ≥65 years worldwide (32). Greater than 80% of people with diabetes also have other NCDs (33), with cardiovascular diseases representing the largest cause of diabetes-related morbidity and mortality (34). In Italy, diabetes affects ∼5.5% of the general population (∼3.5 million people), and the number of Italians with diabetes has increased by ∼60%, from only 3.4% in 1993 (35). As a result, the Italian Health Service estimates spending about €10 billion per year for direct and indirect costs related to diabetes care (36). Notwithstanding the international evidence on the effect and use of MET in primary prevention, in Italy, MET remains the first-line drug for type 2 diabetes treatment; its prescription for prevention in people at high risk of diabetes or with MetS is not a clinical recommendation. Consistently, during the first period of recruitment, we encountered many difficulties. Several general practitioners discouraged people from participating in the MeMeMe trial because MET was proposed to people without diabetes. Our results strongly support the use of MET as a safe and effective treatment to reduce the occurrence of diabetes and to rapidly reverse MetS. Additionally, our study further reinforces previous proposals to revise the clinical indications for MET use (37).

The dietary intervention in the MeMeMe trial was ineffective, and we did not highlight any protection in the participants randomized to the MedDiet, neither for diabetes nor for other NCDs. Compared with the DPP and other diabetes prevention trials based on intensive and multifactorial lifestyle strategies, the MeMeMe intervention, based on a single nutritional activity per month, was not sufficient to induce a significant change in the participants' dietary habits. People in MET+MedDiet intervention, however, significantly improved their metabolic and anthropometric parameters, with a significant decrease in body weight, BMI, waist circumference, glycemia, and LDL cholesterol level compared with the other three groups. Several other randomized controlled trials have demonstrated that MedDiet can



Number at risk						
Placebo	343	300	232	189	109	43
MedDiet	368	330	269	213	130	46
MET	373	319	271	223	142	43
MET+MedDiet	358	316	274	220	130	38

Event/Years	1st year	2nd year	3rd year	4th year	5th year	HR (95% CI) Adjusted
Placebo	4	12	4	0	1	1
MedDiet	4	8	7	7	2	1.23 (0.67- 2.24)
MET	1	1	2	0	1	0.20 (0.10-0.55)*
MET+MedDiet	0	0	1	1	0	0.08 (0.02-0.35)*

HR adjusted for age (quintiles), BMI at baseline (quintiles), and sex.
*$P < 0.05$

Figure 2—Cumulative hazard of type 2 diabetes.

regress MetS (7,8), and it is a useful tool to reduce body weight and obesity-related metabolic alterations (6).

Our results also demonstrated that participants randomized in the MET-alone group significantly improved anthropometric parameters. Metformin increases energy metabolism by upregulating adaptive thermogenesis, inhibiting lipid synthesis, and promoting fatty acid oxidation through the activation of AMPK (38). Metformin also induces the anorexigenic metabolite *N*-lactoyl-phenylalanine in cells (39). To date, the precise mechanisms underlying these beneficial effects on body weight and energy metabolism have not been fully elucidated.

The MeMeMe trial presents some limitations. By study design, participants did not undergo glycosylated hemoglobin or oral glucose tolerance tests at baseline and during the follow-up; only an annual fasting blood sample was collected. However, diabetes was not the primary outcome of the study. As a consequence, we cannot exclude that in the MET groups, some cases of diabetes may have been missed because the treatment masked the diagnosis (hyperglycemia above the diabetes threshold). Additionally, the originally planned target of 1,600 randomized participants was not achieved. However, with 1,442 participants successfully randomized, the study's statistical power was robust.

A potential limitation of using MET for diabetes prevention is that its protective effects may decrease shortly after discontinuation, and evidence of long-term benefits or complications (e.g., cobalamin reduction) remains limited (40). Therefore, we recommended our volunteers in the MET groups to continue the treatment after the conclusion of the study, and we obtained their consent to manage an active clinical follow-up.

Despite its limitations, our study strongly demonstrates that the use of 1,700 mg/day MET is effective to prevent diabetes in people selected for the presence of MetS. The scheduled dose of MET (500 mg/day for the first month, 850 mg/day for the next 2 months, and 1,700 mg/day subsequently) proved to be safe, with only 22 participants (n = 3 in the placebo and 19 in the MET groups) dropping out after randomization (n = 21 for minor gastrointestinal effects and 1 for increase in liver enzyme levels). Our MedDiet intervention alone seemed not to be efficient in reducing diabetes and MetS but was useful if associated with MET consumption, improving the effect of the drug. Further analyses and follow-up of the cohort are needed to understand the impact of MET in the prevention of NCDs in people without diabetes.

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collection and interpretation. I.B., E.B., E.V., A.B., and M.R. contributed to writing the manuscript. M.B. and G.G. contributed to the data collection. F.B. and P.P. are the guarantors of this work and, as such, had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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