Fenofibrate and Metabolic Syndrome

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Supplemental material

Materials and Methods

The maximal sampled population consisted of 1,107 white subjects with no missing phenotypes on 10 traits studied (Table 1). Most of the subjects participated in all clinical visits as part of the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study which, in part recruited from participants of the NHLBI Family Heart Study [85-87]. The GOLDN study is a clinical familial study with two treatment arms, one related to FF treatment and one to a fat-load meal. Our study is focused on examining the effects of FF on the lipid profiles (see Supplemental Figure 2). Subjects came to the clinic for five visits with two intermediate phone calls to check drug safety and compliance. Visit 0 served as a screening visit to obtain consent and test for blood chemistries. In addition, after consultation with and approval of their physicians, subjects were asked to discontinue any prescription, non-prescription and nutraceuticals which may affect lipid levels for a period of at least 4 weeks before our clinical trial. The time between visit 0 and visit 1 served as a washout period of any previous lipid lowering medication. Visit 1 was approximately 4 to 8 weeks after visit 0. Visit 2 (first draw of the blood) was only a day after visit 1, and the average of visit 1 and visit 2 serves as the baseline of the lipid measurements. At

the end of this period FF tablets were dispensed to study participants. Two phone calls, approximately one and two weeks apart after visit 2 were to study subjects in order to verify medication compliance and inquire about tolerance to the study medication. Visit 3 in the clinic was approximately 3 to 4 weeks after visit 2, and visit 4 (first draw of the blood) was one day after visit 3.

Between the initial (visits 1 and 2) and follow-up clinical visits (visits 3 and 4) participants received one tablet of 160 mg/day FF TriCor® medication (Abbott Laboratories, Chicago, IL, USA), (details of the GOLDN design are provided in the Supplemental Figure 2). Ten phenotypes were analyzed in our study, body mass index (**BMI**- kg/m^2), waist circumference (**WAIST**- cm), waist-to-hip ratio (**WHR**), plasma insulin (**INS**-mu/l), plasma glucose (**GLUC**-mg/dL), **TG** (mg/dL), **LDLC** (mg/dL), **HDLC** (mg/dL), systolic- and diastolic blood pressure (**SBP**, **DBP-** mm Hg). Only three of them, TG, HDLC, and LDLC combined with INS were the main contributors in a factor, which was named by us as **lipids MetS domain**. This domain and its change represent the main focus of our study (see Statistical Analysis). Weight was measured at baseline and also after the FF treatment with a beam balance. Height was measured without shoes with fixed stadiometer. The other anthropometric- and blood pressure measurements were collected from all participants at the baseline visit. WHR was calculated as the ratio of waist measured at the level of umbilicus divided by hip circumference measured at the maximal hip girth. Plasma insulin was quantified by the Human Insulin Specific RIA Kit (Linco Research). Plasma glucose was measured with the method of hexokinase-mediated reaction on a Hitachi 911 (Roche Diagnostics). Blood pressure was measured as the average of two consecutive sitting measurements after a five-minute rest, with an oscillometric device

(Dinamap Pro Series 100, GE Medical Systems) and Critikon^{TM} blood pressure cuffs by Johnson & Johnson.

The biochemical measurements were collected before and after FF treatment. TG was measured by glycerol-blanked enzymatic method (Trig/GB, Roche Diagnostics Corporation, Indianapolis, IN) on the Roche /Hitachi 911 Automatic Analyzer. The HDLC was measured, after precipitation of non-HDLC with magnesium/dextran, on the Hitachi 911 using an esterase, oxidase reaction (Chol R1, Roche Diagnostics Corporation). LDLC was measured by a homogeneous direct method (LDLC, Direct Liquid Select™ Cholesterol Reagent, Equal Diagnostics, Exton, PA) on the Hitachi 911. Participants were asked to fast for 12 hours before a clinical visit. If subjects fasted less than 8 hours we excluded that particular subject's measurements from our analysis. The GOLDN study had genotyped 29 candidate genes, with a total of 115 SNPs selected for important polymorphisms in the Nutrition and Genomics Laboratory of the Tuft University, Boston, MA. The methodology of the SNPs genotyping is described in detail in previous published papers [90-92].

The study participants who had a history of liver, kidney, pancreas, or gall bladder disease, or malabsorption, or currently used insulin, were also excluded. Participants were >= 18 years of age, and withdrew the lipid-lowering medications at least four weeks prior to the initial clinical visit. Written informed consent was obtained from each participant.

Statistical analysis

TG and INS were log transformed; GLUC was transformed as the inverse of the squared value ($1/GLUC^2$) to achieve a normal distribution. The 10 variables were adjusted for age, age^2, and age^3 in a step-wise regression when significant age contributions within gender were present. Factor analysis (FA) was performed for each visit on the 10 residuals of the adjusted variables.

The factor analysis model is $\boldsymbol{x} = \boldsymbol{\lambda f} + \boldsymbol{\varepsilon}$ where **x** represents a *p*–element row-vector of real variables studied, $\boldsymbol{\lambda}$ is a *p x k* matrix of *loadings*, $\boldsymbol{f}$ is a *k*–element vector of *scores* and $\boldsymbol{\varepsilon}$ - a *p*–element vector of errors. Only $\boldsymbol{x}$ is observed. The analysis was performed with the FACTANAL function of Splus 8.0, operated in batch mode through Cygwin installed on the Microsoft Windows OS Vista Professional. The maximum likelihood method and Varimax rotation were the selected options to fit the appropriate model. Variables measured only once, as for example WAIST, (assumed not to change much during the study period), were repeated as the same variable in all other visits factor analyses. BMI before the treatment was repeated as the same for all other visits before treatment, and BMI of visit 3 (after treatment) was repeated as the same variable at visit 4. Only lipid variables were measured at each visit, therefore our focus was only on the MetS lipids domain. The rest of the variables are used only to construct a particular factor analysis (See Supplemental Figure 3 for their correlation pattern). Factor scores for the MetS lipids domain, for each subject, and for each visit were produced. (See Supplemental Figure 4)

In addition, random coefficients model (RCM) was performed in SAS by creating a treatment class variable which differentiated factor scores of visits 1 and 2 as before treatment, and factor scores of visits 3 and 4 as after treatment. This class variable was used in the repeated statement of the mixed model in SAS to produce the random intercepts and slopes for each subject. The model is $y_{ij} = \alpha + \beta x_{ij} + a_i^* + b_i^* x_{ij} + \varepsilon_{ij}$ where with * are indexed the random intercepts a, and random slopes b for the i-subject. Slopes for each subject (b_i^*) represent the response change before (visits 1 and 2) versus after FF treatment (visits 3 and 4).

The factor scores for the MetS lipids domain for each visit, as well as the random slopes were utilized as response phenotypes in the linear mixed model to assess the association among the response phenotypes and 115 SNPs of 29 candidate genes. The linear mixed effects models

to test association between factor scores and SNPs polymorphisms were applied in SAS 9.1.3. The mixed statistical model was built on the additive SNP genetic model as fixed effect and pedigree memberships as a random effect to account for the correlations within a pedigree in the variance covariance matrix. In a matrix form the mixed model is $\boldsymbol{y}=\boldsymbol{X\beta}+\boldsymbol{Zu}+\boldsymbol{e}$, where $\boldsymbol{y}$- was a vector of factor scores from each FA, or a vector of random slopes from the RCM; $\boldsymbol{X}$- was the design matrix with recoded genotypes based on the additive genetic model where each SNP was evaluated for its fixed effect $\boldsymbol{\beta}$; $\boldsymbol{Z}$-was the design matrix for the random pedigree effects measured through the random effects vector $\boldsymbol{u}$; and $\boldsymbol{e}$- was the error vector. In the association tests we applied the option DDFM=KR of degrees of freedom, which specifies the method for computing the denominator degrees of freedom for the tests of fixed effects [107].

Following are **Supplemental Tables 1-7 and Supplemental Figures 1-4**.

Supplemental Table 1. Clinical Trials for TriCor® (Fenofibrate)

First Author	Journal	Baseline (mg/dL)	Age (years)	Duration (weeks)	Ethnicity/ Country	No. of pts	Dosage (mg/day)	Lipid After Treatment (mg/dL) LDLC	HDLC	TG
Filippatos TD.	Diabetes Obes Metab. (2008)	LDLC 157 HDLC 51 TG 240	54	26	Greece	28	200	137	53	156
Rosenson RS.	Am Heart J (2008)	LDLC 139 HDLC 31 TG 295	52	13	USA	25	160	131	35	157
Arca M.	Metabolism (2007)	LDLC 176 HDLC 45 TG 307	30-75	24	Italy	29	200	136	51	132
Farnier M.	Am Heart J (2007)	LDLC 163 HDLC 46 TG 231	55	12	White 79% Hispanic 13% Black 2% Other 6%	184	160	138	54	136
Franceschini G.	Atherosclerosis (2007)	LDLC 114 HDLC 32 TG 287	56	8	Italy	26	160	123	40	164
Hiukka A.	Diabetologia (2007)	LDLC 128 HDLC 43 TG 133	62	5 years	Finland	87	200	104	43	97
Ryan KE.	Atherosclerosis (2007)	LDLC 128 HDLC 44 TG 188	46	12	UK	16	160	119	48	123
Davidson MH.	Clin Cardiol (2006)	LDLC 121 HDLC 36 TG 480	57	8	White 93% Black 4% Other 3%	96	130	139	41	304
Zhu S.	Clin Chem (2006)	LDLC 129 HDLC 51 TG 212	60	104	Canada	115	160	116	61	153
Undas A.	Thromb Haemost (2005)	LDLC 151 HDLC 62 TG 190	52	4	Poland	22	160	132	74	128
Ducobu J.	J Cardio Pharm (2003)	LDLC 203 HDLC 41 TG 181	54	13	France	75	200	167	46	111
Wang TD.	Atherosclerosis (2003)	LDLC 143 HDLC 41 TG 265	61	8	Taiwan	35	200	127	45	137

Feher MD.	Diabetes Metab Res Rev. (1999)	LDLC 186 HDLC 50 TG 266	62	12	UK	16	200	145	60	149
The Field investigators.	Lancet. (2005)	LDLC 120 HDLC 43 TG 155	62	136	Australia New Zealand Finland	4,895	200	95	44	131

Suppl. Table 2. Mixed model additive effect: Lipids factor time 0

RS_number*	Markname	DenDF	ProbF	Estimate	StdErr	RSquare	Chrom	Position	Al1	MAF	Al2
rs662799	APOA5_M1123	1102	6.29E-06	0.3253	0.07167	0.018471	11	116168917	3	6.05	1
rs3135506	APOA5_S16W	1104	1.68123E-05	0.31	0.07172	0.016727	11	116167617	2	6.08	3
rs1800590	LPL_M107	1104	2.02133E-05	-0.5117	0.1195	0.016442	8	19840951	3	1.97	4
rs5128	APOC3_3U386	1103	2.80315E-05	0.2441	0.05804	0.016032	11	116208850	3	9.4	2
rs1801177	LPL_D9N	1104	5.85099E-05	0.5849	0.145	0.014613	8	19849988	1	1.51	3
rs11703495	PPARARS11703495	1104	8.77934E-05	0.2285	0.05804	0.013966	22	44913855	4	9.53	1
rs4520	APOC3_G34G	1104	9.90489E-05	0.1465	0.03749	0.013774	11	116206745	4	26.89	2
rs5104	APOA4_N147S	1102	0.000341345	0.1732	0.04822	0.011724	11	116197544	3	13.43	1
rs4253728	PPARARS4253728	1096	0.001811693	-0.1244	0.03978	0.00903	22	44930586	1	22.77	3
rs2854117	APOC3_M482	1101	0.002258837	-0.1201	0.03924	0.008552	11	116205352	1	24.87	3
rs8138102	PPARARS8138102	1102	0.004046678	0.1245	0.04322	0.007653	22	44912271	3	19.2	1
rs2727784	APOA1_M2803	1102	0.010976789	0.09106	0.03574	0.005893	11	116216351	3	35.54	1
rs613808	APOA1_M2630	1104	0.011747801	-0.09407	0.03727	0.005812	11	116216178	1	29.68	3
rs5092	APOA4_T29T	1102	0.014056662	0.1086	0.04416	0.005575	11	116198674	3	17.4	1
rs135543	PPARARS135543	1100	0.020646401	0.08394	0.03621	0.004951	22	44875840	1	31.54	3
rs9626730	PPARARS9626730	1098	0.031333039	0.1003	0.04654	0.00434	22	44882702	2	15.22	4
rs429358	APOE_C130R	1103	0.041152052	-0.09181	0.04491	0.00391	19	50103781	2	16.55	4
rs676210	APOB_P2739L	1100	0.044919457	-0.08322	0.04145	0.003771	2	21143176	1	21.4	3
rs4289236	ABCG5_I11836	1097	0.046707291	0.08317	0.04177	0.003662	2	43965774	1	19.97	3
rs268	LPL_N291S	1103	0.049637668	0.2866	0.1458	0.003577	8	19857809	3	1.36	1

Note:*RS_number-dbSNP rs name; Markname-marker name; DenDF-denominator degrees of freedom; ProbF-p value of the F statistic test; Estimate-beta coefficient estimated effect; StdErr- standard error of the estimated effect; RSquare-R-square statistic; Chrom- chromosome; Position-location in base pairs in a chromosome; Al1- allele 1; MAF-minor allele frequency; Al2- allele 2.

Suppl. Table 3. Mixed model additive effect: Lipids factor time 1

RS_number*	Markname	DenDF	ProbF	Estimate	StdErr	RSquare	Chrom	Position	Al1	MAF	Al2
rs8138102	PPARARS8138102	790	0.000270277	0.1893	0.05173	0.016892	22	44912271	3	19.2	1
rs11703495	PPARARS11703495	791	0.000277992	0.2455	0.06723	0.016791	22	44913855	4	9.53	1
rs3135506	APOA5_S16W	791	0.000323282	0.3186	0.08822	0.016296	11	116167617	2	6.08	3
rs1801177	LPL_D9N	791	0.000869937	0.6378	0.1908	0.01405	8	19849988	1	1.51	3
rs4253728	PPARARS4253728	787	0.001247784	-0.1559	0.04812	0.013429	22	44930586	1	22.77	3
rs1800590	LPL_M107	790	0.004561984	-0.4429	0.1557	0.010279	8	19840951	3	1.97	4
rs9626730	PPARARS9626730	788	0.005160345	0.1587	0.05657	0.010112	22	44882702	2	15.22	4
rs135543	PPARARS135543	789	0.006304371	0.122	0.04456	0.009489	22	44875840	1	31.54	3
rs662799	APOA5_M1123	789	0.007464295	0.2401	0.0895	0.009428	11	116168917	3	6.05	1
rs5128	APOC3_3U386	790	0.011347549	0.1914	0.07541	0.008574	11	116208850	3	9.4	2
rs2854117	APOC3_M482	789	0.015477798	-0.1174	0.04838	0.007713	11	116205352	1	24.87	3
rs6507931	LIPG_I24582	791	0.017126061	0.0991	0.04148	0.007187	18	45367006	2	44.97	4
rs405509	APOE_M226	791	0.020769115	0.09828	0.04242	0.006835	19	50100676	1	48.83	2
rs715948	LRP1_I10701	789	0.021669958	-0.1019	0.04428	0.006963	12	55819249	1	31.09	3
rs135550	PPARARS135550	787	0.022245391	-0.1052	0.04591	0.00669	22	44873753	3	28.72	1
rs4520	APOC3_G34G	791	0.027591278	0.1034	0.04685	0.00628	11	116206745	4	26.89	2
rs5090	APOA4_M35	791	0.029582924	0.2169	0.09953	0.006016	11	116199265	3	5.14	2
rs2276269	LIPG_I13576	791	0.03029449	-0.09013	0.04153	0.005943	18	45356000	4	44.63	2
rs1981429	SDC4_I1372	788	0.030684819	0.09197	0.04248	0.00608	20	43409107	1	49.96	2
rs3736265	PPARGC1A_T612M	791	0.032919526	0.1984	0.09283	0.005916	4	23490976	1	5.82	3
rs5104	APOA4_N147S	790	0.035122907	0.129	0.06113	0.005952	11	116197544	3	13.43	1
rs268	LPL_N291S	791	0.0384302	0.3876	0.1869	0.005537	8	19857809	3	1.36	1
rs2727784	APOA1_M2803	790	0.038588176	0.09112	0.04397	0.005474	11	116216351	3	35.54	1
rs1042031	APOB_E4181K	790	0.047492709	0.1115	0.05616	0.005135	2	21137405	1	16.94	3

*See Suppl. ***Table 2*** note.

Suppl. Table 4. Mixed model additive effects, Lipids factor time 2

RS_number*	Markname	DenDF	ProbF	Estimate	StdErr	RSquare	Chrom	Position	Al1	MAF	Al2
rs662799	APOA5_M1123	1103	1.88E-06	0.3588	0.07487	0.02049	11	116168917	3	6.05	1
rs5128	APOC3_3U386	1104	7.48E-06	0.2727	0.06059	0.018252	11	116208850	3	9.4	2
rs1801177	LPL_D9N	1105	8.76852E-05	0.589	0.1496	0.013868	8	19849988	1	1.51	3
rs4520	APOC3_G34G	1105	9.08716E-05	0.1542	0.03926	0.013852	11	116206745	4	26.89	2
rs5104	APOA4_N147S	1103	0.000100182	0.1965	0.05032	0.013754	11	116197544	3	13.43	1
rs3135506	APOA5_S16W	1105	0.000109566	0.2912	0.07501	0.013497	11	116167617	2	6.08	3
rs2854117	APOC3_M482	1102	0.000210086	-0.152	0.04087	0.012491	11	116205352	1	24.87	3
rs1800590	LPL_M107	1104	0.000273701	-0.4578	0.1254	0.011968	8	19840951	3	1.97	4
rs9626730	PPARARS9626730	1099	0.00066428	0.1657	0.04854	0.010591	22	44882702	2	15.22	4
rs135543	PPARARS135543	1101	0.001101992	0.1239	0.03787	0.009663	22	44875840	1	31.54	3
rs5092	APOA4_T29T	1103	0.001655324	0.1452	0.04605	0.009034	11	116198674	3	17.4	1
rs11703495	PPARARS11703495	1105	0.002343937	0.1856	0.06087	0.008411	22	44913855	4	9.53	1
rs2727784	APOA1_M2803	1103	0.003082033	0.1109	0.03739	0.007922	11	116216351	3	35.54	1
rs4253728	PPARARS4253728	1097	0.005266108	-0.1164	0.04165	0.007139	22	44930586	1	22.77	3
rs8138102	PPARARS8138102	1103	0.006398873	0.1236	0.04524	0.006845	22	44912271	3	19.2	1
rs135550	PPARARS135550	1098	0.0085137	-0.1036	0.0393	0.006353	22	44873753	3	28.72	1
rs676210	APOB_P2739L	1101	0.01688377	-0.1037	0.04335	0.005232	2	21143176	1	21.4	3
rs613808	APOA1_M2630	1105	0.017607096	-0.09284	0.03905	0.005126	11	116216178	1	29.68	3
rs934197	APOB_M516	1105	0.026743899	0.08382	0.03779	0.004463	2	21179113	1	33.57	3
rs1284300	PDZK1_I4201	1105	0.031583956	0.1378	0.06401	0.004197	1	143236507	4	8.65	2
rs1263177	APOA4_A5INTER	1101	0.044833442	-0.0746	0.03714	0.003787	11	116180028	2	35.08	4

*See Suppl. ***Table 2*** note.

Suppl. Table 5. Mixed model additive effects, Lipids factor time 3

RS_number	Markname	DenDF	ProbF	Estimate	StdErr	RSquare	Chrom	Position	Al1	MAF	Al2
rs1801177	LPL_D9N	775	0.000437106	0.7504	0.2125	0.015857	8	19849988	1	1.51	3
rs11703495	PPARARS11703495	775	0.00334152	0.2221	0.07546	0.011099	22	44913855	4	9.53	1
rs1800590	LPL_M107	774	0.004037807	-0.5173	0.1794	0.010649	8	19840951	3	1.97	4
rs135543	PPARARS135543	773	0.004351251	0.1428	0.04994	0.010471	22	44875840	1	31.54	3
rs9626730	PPARARS9626730	773	0.006440856	0.1766	0.06466	0.009602	22	44882702	2	15.22	4
rs1042031	APOB_E4181K	774	0.006628356	0.1733	0.06367	0.009512	2	21137405	1	16.94	3
rs4253728	PPARARS4253728	771	0.006990036	-0.1462	0.05407	0.009473	22	44930586	1	22.77	3
rs662799	APOA5_M1123	773	0.010410825	0.2605	0.1015	0.008607	11	116168917	3	6.05	1
rs5104	APOA4_N147S	774	0.010523085	0.1759	0.06859	0.008566	11	116197544	3	13.43	1
rs8138102	PPARARS8138102	774	0.011562718	0.1476	0.05832	0.008261	22	44912271	3	19.2	1
rs5128	APOC3_3U386	774	0.017302904	0.2023	0.08481	0.007482	11	116208850	3	9.4	2
rs4148217	ABCG8_T400K	772	0.021140344	-0.138	0.05973	0.006866	2	44011084	1	19.19	2
rs5092	APOA4_T29T	774	0.027431312	0.1406	0.06362	0.006352	11	116198674	3	17.4	1
rs268	LPL_N291S	775	0.028518446	0.4569	0.2082	0.006193	8	19857809	3	1.36	1
rs135550	PPARARS135550	771	0.029155538	-0.1125	0.05146	0.006158	22	44873753	3	28.72	1
rs3808607	CYP7A1_M203	771	0.029574279	-0.1038	0.04762	0.006218	8	59575478	3	42.41	4
rs4520	APOC3_G34G	775	0.032226913	0.1127	0.05255	0.005937	11	116206745	4	26.89	2
rs12497191	PPARG_M2823	775	0.036413221	0.1512	0.07214	0.005661	3	12365135	3	12.84	1
rs1800783	NOS3_I1103	771	0.040320653	0.1014	0.04936	0.005466	7	150127045	1	37.77	4
rs2854117	APOC3_M482	773	0.045831187	-0.1091	0.05453	0.005261	11	116205352	1	24.87	3

*See Suppl. ***Table 2*** note.

Suppl. Table 6. Mixed model additive effects, Lipids factor time 4

RS_number	Markname	DenDF	ProbF	Estimate	StdErr	RSquare	Chrom	Position	Al1	MAF	Al2
rs11703495	PPARARS11703495	781	0.000457621	0.272	0.07729	0.015789	22	44913855	4	9.53	1
rs662799	APOA5_M1123	779	0.001495072	0.3325	0.1043	0.012932	11	116168917	3	6.05	1
rs1801177	LPL_D9N	781	0.002405703	0.6687	0.2196	0.012025	8	19849988	1	1.51	3
rs135543	PPARARS135543	779	0.005357472	0.1435	0.0514	0.010332	22	44875840	1	31.54	3
rs8138102	PPARARS8138102	780	0.005762646	0.1659	0.05993	0.009911	22	44912271	3	19.2	1
rs1800783	NOS3_I1103	777	0.006650408	0.1377	0.05059	0.009679	7	150127045	1	37.77	4
rs3808607	CYP7A1_M203	777	0.007007322	-0.1323	0.04893	0.009455	8	59575478	3	42.41	4
rs4253728	PPARARS4253728	777	0.007054756	-0.1503	0.05564	0.009463	22	44930586	1	22.77	3
rs1042031	APOB_E4181K	780	0.010259766	0.1683	0.06541	0.008654	2	21137405	1	16.94	3
rs5104	APOA4_N147S	780	0.012524054	0.1768	0.07065	0.008053	11	116197544	3	13.43	1
rs5128	APOC3_3U386	780	0.014760746	0.2135	0.08736	0.007651	11	116208850	3	9.4	2
rs5092	APOA4_T29T	780	0.019970457	0.1526	0.06547	0.007057	11	116198674	3	17.4	1
rs2854117	APOC3_M482	779	0.021354998	-0.1294	0.05611	0.006908	11	116205352	1	24.87	3
rs4520	APOC3_G34G	781	0.022555269	0.1235	0.05406	0.006883	11	116206745	4	26.89	2
rs2727784	APOA1_M2803	779	0.023554588	0.1158	0.05102	0.006903	11	116216351	3	35.54	1
rs135550	PPARARS135550	777	0.027077584	-0.1172	0.05294	0.006785	22	44873753	3	28.72	1
rs12497191	PPARG_M2823	781	0.027082911	0.1641	0.07409	0.006497	3	12365135	3	12.84	1
rs429358	APOE_C130R	780	0.030170565	-0.135	0.06216	0.006164	19	50103781	2	16.55	4
rs715948	LRP1_I10701	779	0.037989444	-0.1071	0.0515	0.005642	12	55819249	1	31.09	3
rs9626730	PPARARS9626730	779	0.040288229	0.1358	0.0661	0.005587	22	44882702	2	15.22	4
rs1800590	LPL_M107	780	0.041396175	-0.366	0.1792	0.005655	8	19840951	3	1.97	4
rs268	LPL_N291S	781	0.042012451	0.4377	0.2149	0.005566	8	19857809	3	1.36	1
rs701106	SCARB1_I82699	781	0.044582865	-0.1267	0.06299	0.005388	12	123790516	1	17.15	3
rs6507931	LIPG_I24582	781	0.04777362	0.09522	0.04803	0.005524	18	45367006	2	44.97	4
rs676210	APOB_P2739L	778	0.048233992	-0.1145	0.05788	0.005211	2	21143176	1	21.4	3

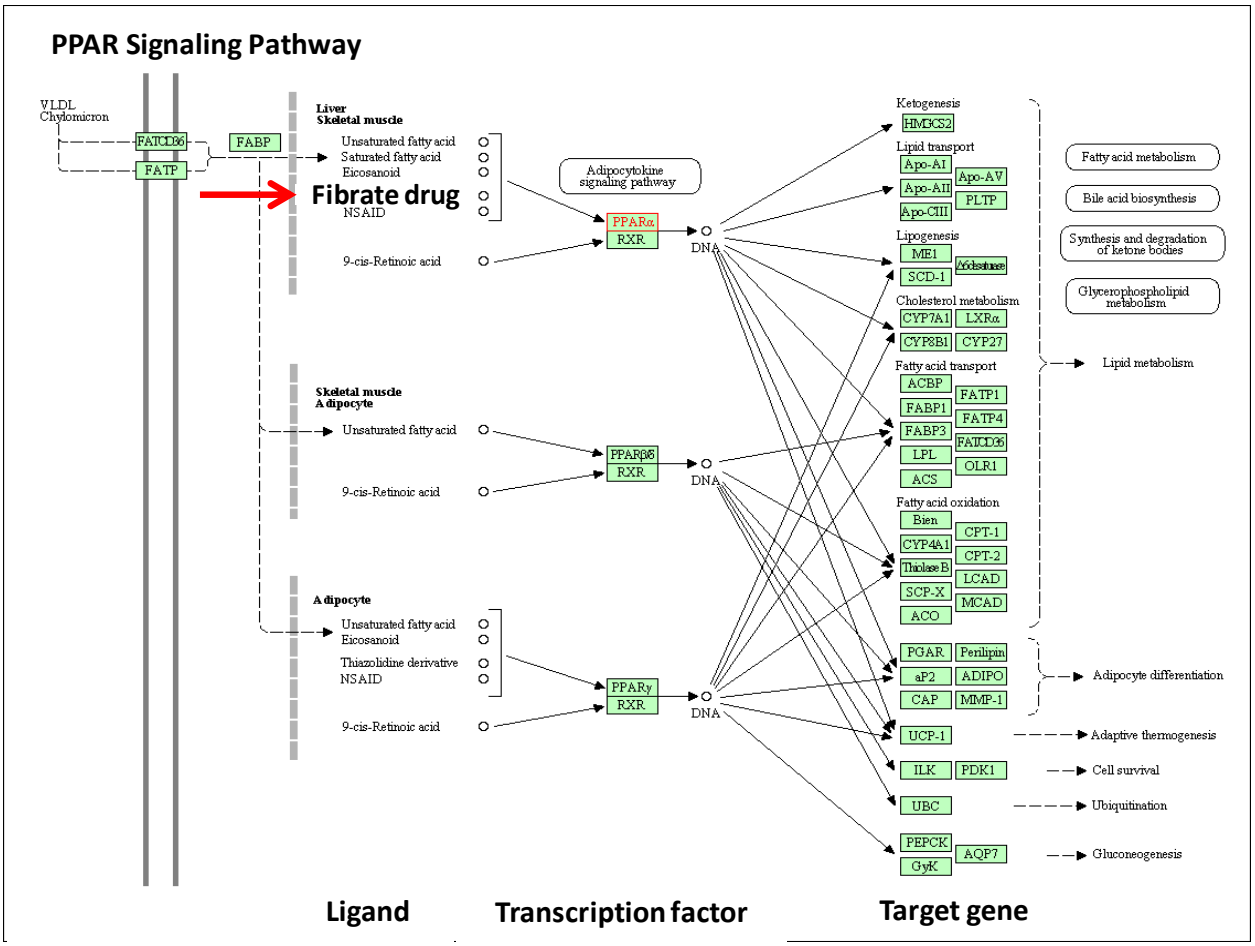
*See Suppl. ***Table 2*** note.

Suppl. Table 7. Mixed model additive effects, Lipids factors RCM beta coefficients associations

RS_number	Markname	DenDF	ProbF	Estimate	StdErr	RSquare	Chrom	Position	Al1	MAF	Al2
rs1799983	NOS3_E298D	1104	8.67509E-05	0.007229	0.001835	0.015007	7	150133759	4	31.85	3
rs1800783	NOS3_I1103	1101	0.000104896	-0.00697	0.001791	0.015	7	150127045	1	37.77	4
rs743507	NOS3_I19342	1105	0.000598674	-0.00686	0.001993	0.011853	7	150145136	3	25.59	1
rs3811800	MTP_M1498	1102	0.01410056	-0.0045	0.001832	0.006613	4	100851731	3	32.1	1
rs4148217	ABCG8_T400K	1102	0.016947961	0.005215	0.002181	0.006191	2	44011084	1	19.19	4
rs6857641	FABP2_M193	1104	0.023281394	-0.00398	0.001752	0.005796	4	120601114	4	42.18	2
rs4697046	PPARGC1A_I55301	1104	0.032026439	-0.00381	0.001774	0.005214	4	23512669	2	37.83	4

*See Suppl. ***Table 2*** note.

Supplemental Figure 1. PPAR pathway (source KEGG). Fibrate drugs serve as a ligand to PPAR-α, which in combination with RXR gene activates several genes part of the lipid metabolism.

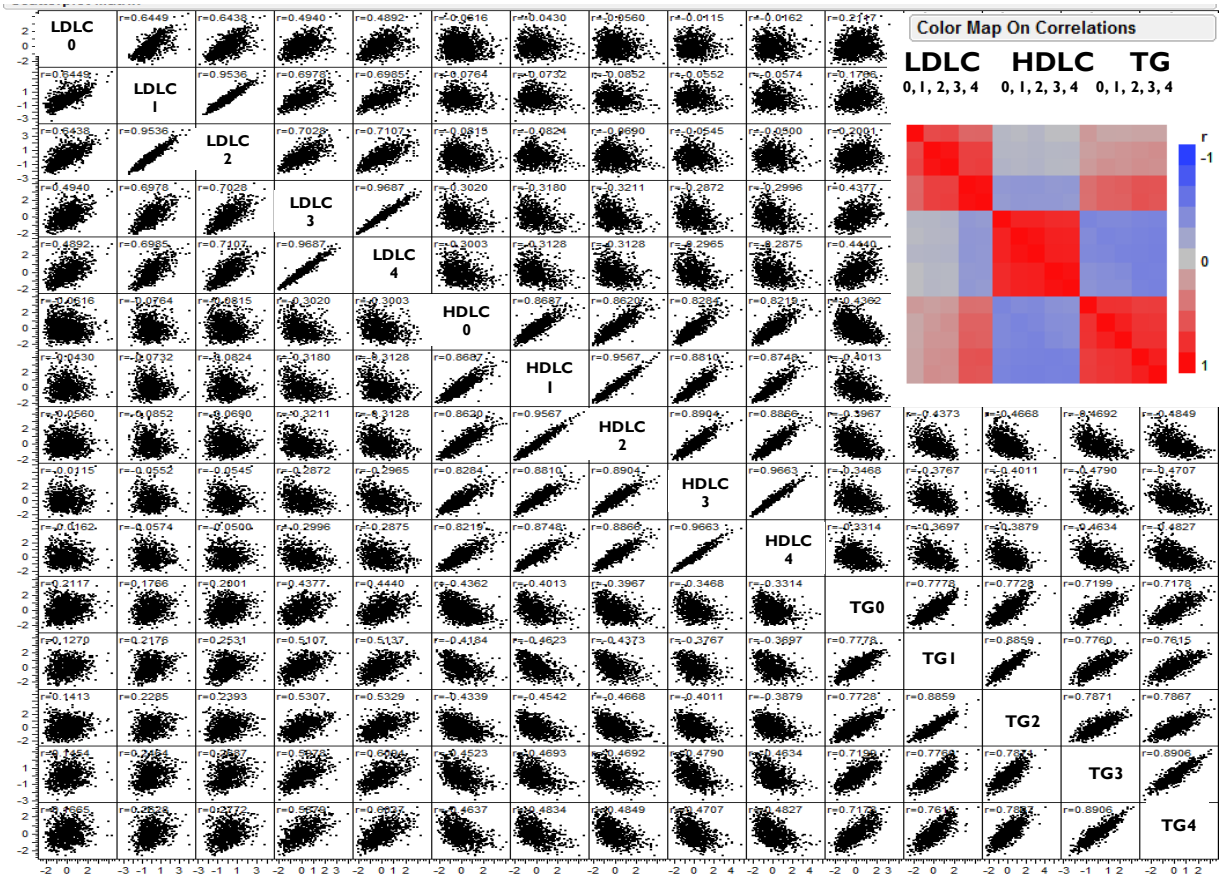


Supplemental Figure 2. The fenofibrate arm in the GOLDN design. Subjects participated in 5 clinical visits, in which among others important lipid variables were measured. The period between visit 0 and visit 1 served as a washout period from any previous lipid lowering drugs. After visit 2, participants took a tablet of 160 mg/day TriCor® (fenofibrate).

Visit	**0**	**1**	**2**	**3**	**4**
Time	Start	4-8 weeks	1 day (draw 1)	3-4 weeks	1 day (draw1)
Phenotypes measured and important events	**TG, HDLC, LDLC** Subjects taken off any lipid-lowering medication	**BMI. WAIST, WHR, INS, GLUC, SBP, DBP, TG, HDLC, LDLC**	**TG, HDLC, LDLC** **Fenofibrates dispensed** Two phone calls follow-up for medication compliance	**BMI, INS, GLUC, TG, HDLC, LDLC**	**TG, HDLC, LDLC**
N (Full set)	**1,107**	**793**	**1,108**	**777**	**783**

Days	**1**	**43**	**44**	**69**	**70**
	Washout Period	**TRT=0**		**TRT=1**	

Supplemental Figure 3. Correlations of lipids variables before (visits 0, 1, 2) and after (visits 3, 4) fenofibrate treatment. It is quite clear that observations measured one day apart (visits 1 and 2, and visits 3 and 4) are very highly correlated for the same lipid variable. The correlation triangle, as well as their color coded correlation shows the clear trend that measurements of lipids for the same subjects were of high quality.



Supplemental Figure 4. Factor structure of the metabolic syndrome lipids domain. The vertical bars represent loadings of variables into the lipids factor. Before treatment (visit 0, 1, and 2) TG, HDLC and INS were the major contributors into MetS lipids domain. After fenofibrate treatment LDLC became also an important contributor in this factor structure.