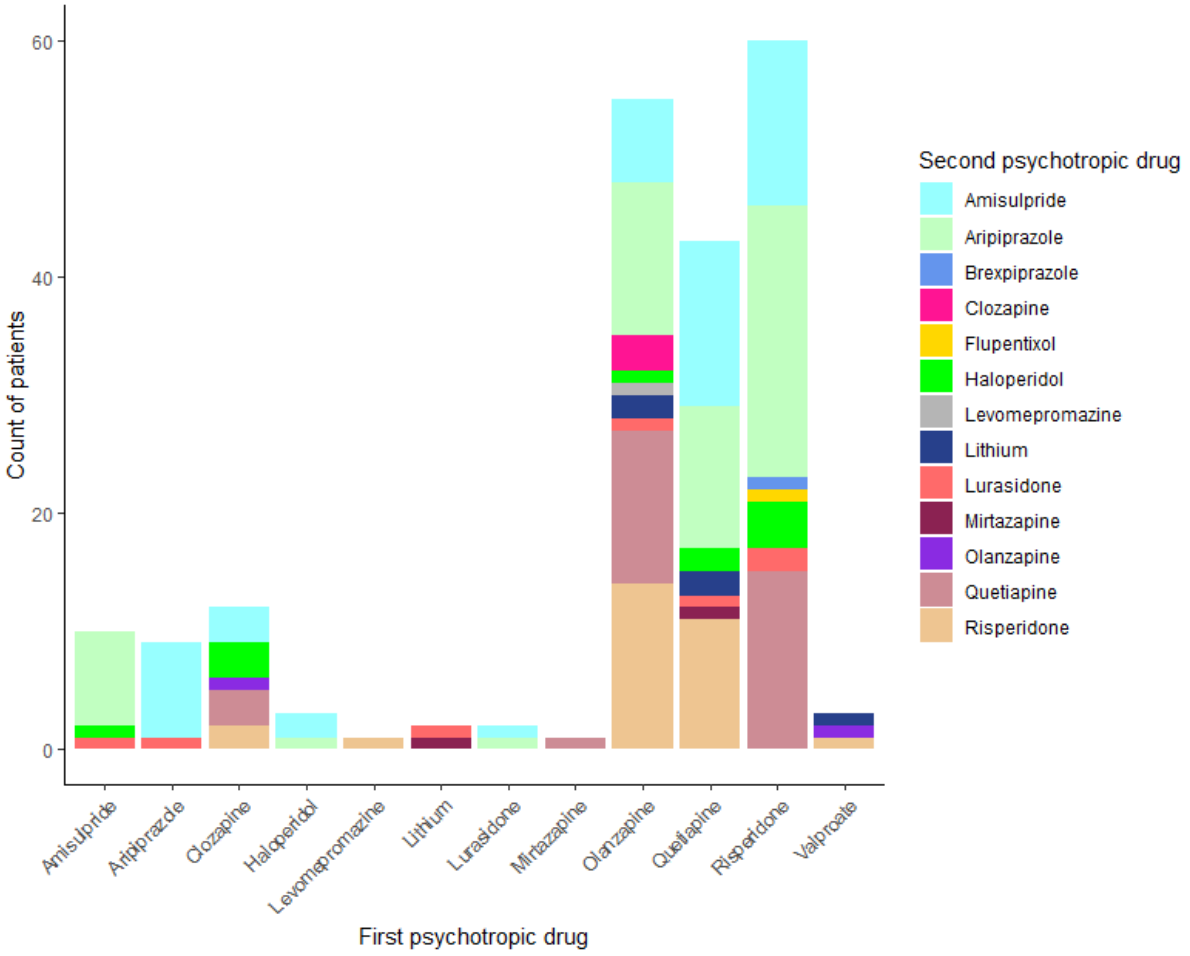
Online Supplement

Supplementary Figure 1. First and second psychotropic drug repartition of patients switching drugs[a].



[a]*Patients taking paliperidone were classified with patients taking risperidone.*

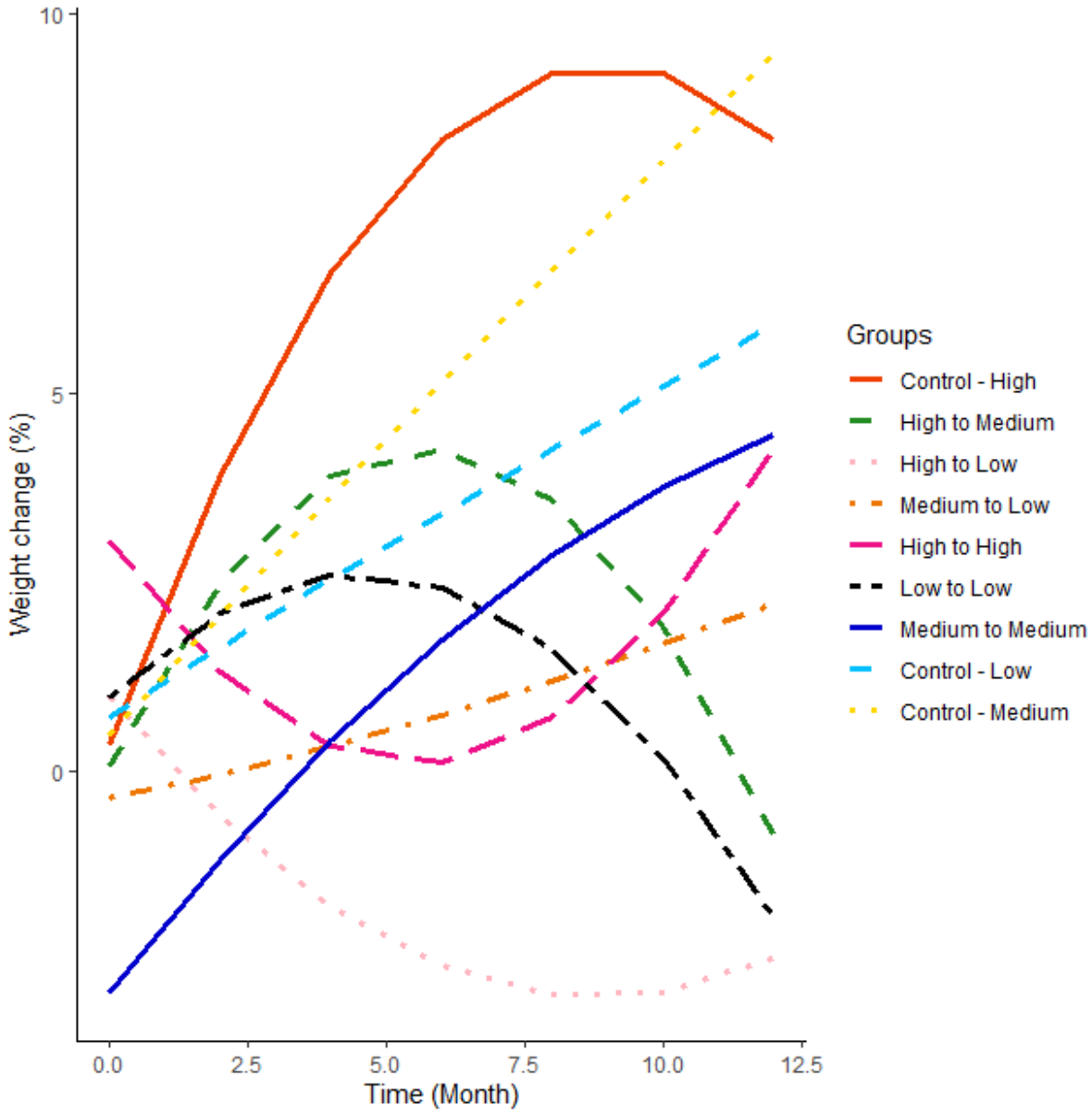
Supplementary Methods.

SNP selection and genotyping.

DNA was extracted from blood samples as described by the manufacturer's protocols using the Flexigene DNA kit and the QIAamp DNA Blood Mini QIAcube Kit (Qiagen AG, Switzerland). Genetic variants were determined by standard genotyping or imputation methods. DNA samples from all patients were genotyped using the Illumina Global Screening Array and processed on an iScan equipped platform (Illumina, San Diego, CA) at the iGE3 genomics platform of the University of Geneva (http://www.ige3.unige.ch/genomics-platform.php).

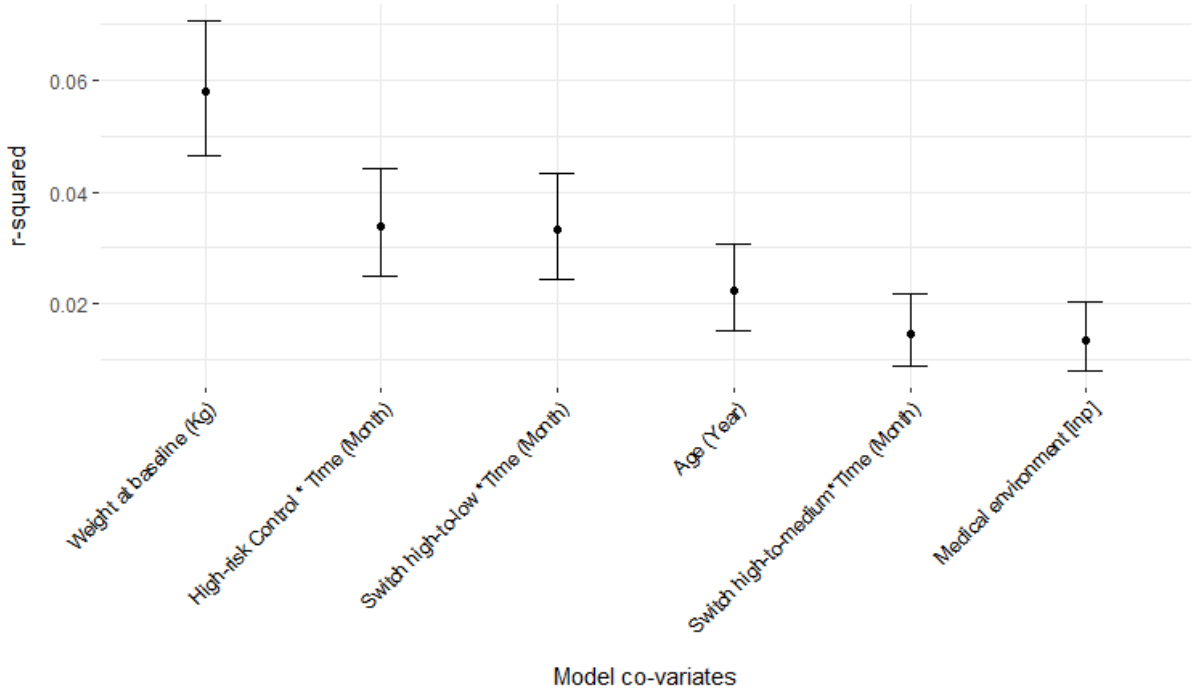
A total of 941 and 97 BMI-associated SNPs in the general population reaching genome-wide significance, 63 BMI and schizophrenia-associated, 17 BMI and bipolar disorder-associated and 32 BMI and major depression-associated SNPs at conjunctional false discovery rate less than 0.01 were combined into five distinct polygenic risk scores[1-3], from which allele effects were used to assign weights to each variant for the calculation of genetic risk scores in the psychiatric samples. In the present study, genetic risk scores were constructed as a weighted sum of all SNPs. Each patient received for each SNP the coding value of 0, 1 or 2 according to the number of risk alleles. For instance, for a given SNP, a score of 1 was assigned for a carrier of one risk allele, whereas a value of 0 was attributed to non-carriers of this risk allele. Weighted GRSs were subsequently obtained by the summation of the BMI-associated risk alleles multiplied by their effect size reported for each SNP, assuming that each SNP contributes to the genetic risk score in an additive way. In order to facilitate results interpretation, wGRSs were then rescaled according to a calculation described elsewhere [4]. Of note, increasing the wGRS by one unit indicates one additional BMI-association risk allele [5]. All quality control (QC) and filtering steps were performed in PLINK [6]. Ancestry was determined using snpweights, a software for inferring genome-wide (GW) ancestry using SNP weights precomputed from large external reference panels[7]. Only individuals of European ancestry were considered in the present study.

Supplementary Figure 2. Evolution of weight changes over time during the first year of treatment (start or switch of treatment).



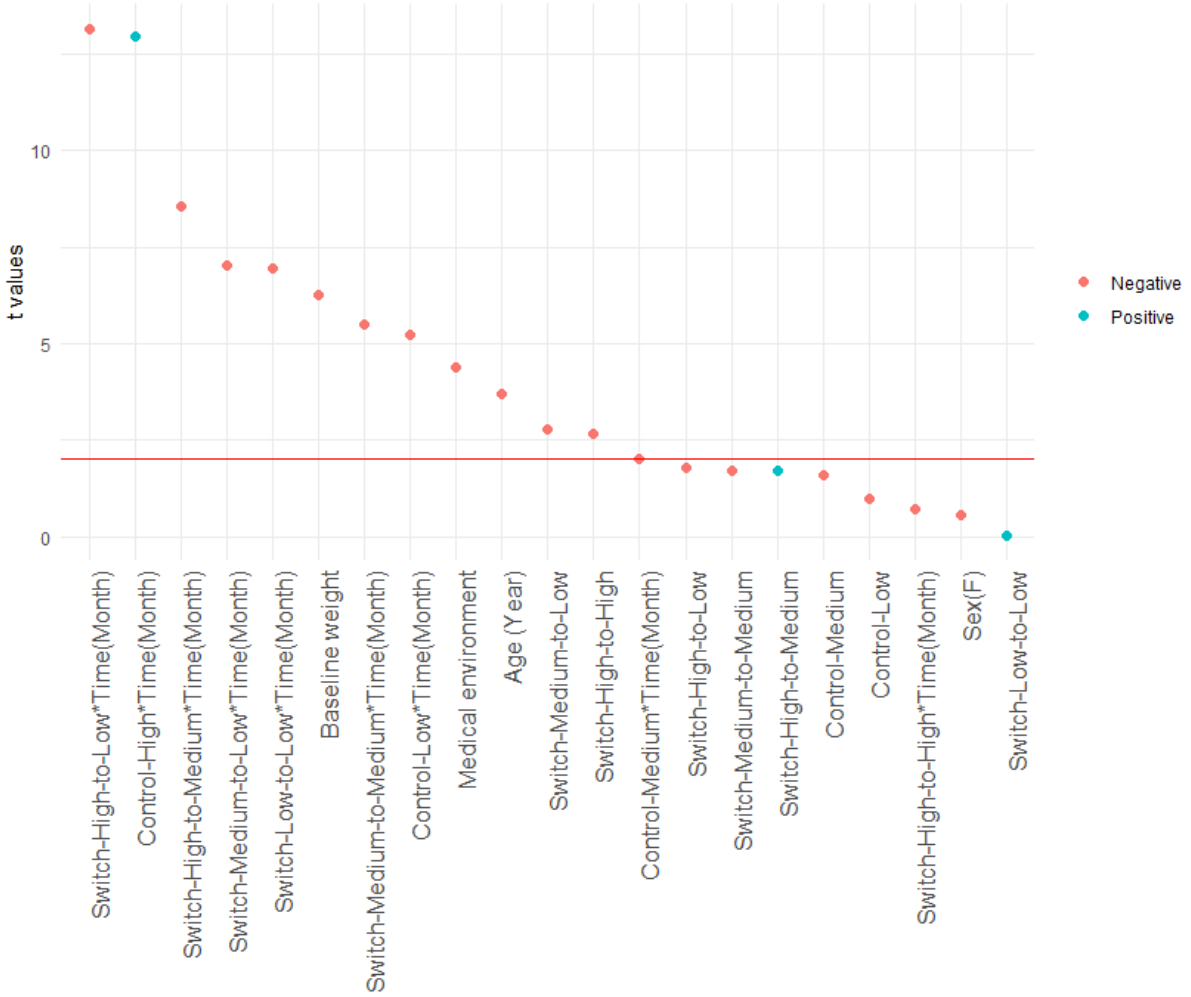
Among patients switching high-to-low and their controls, the greatest loss or increase of weight, respectively, is observed during the first six months.

Supplementary Figure 3. Partial *r*-squared values of linear mixed-effect model of weight change for the first six covariates.



Partial r-squared values for the first six co-variates of linear mixed-effect model of weight change, adjusting by sex, age at baseline, baseline weight, medical environment and by the interaction of both switch and control categories with time.
Abbreviations: inp: inpatients

Supplementary Figure 4. Importance of variables according to the t-statistics of linear mixed-effect model of weight change.



*T-statistic values and co-variates of linear mixed-effect model of weight change, adjusting by sex, age at baseline, baseline weight, medical environment and by the interaction of both switch and control categories with time. Dots over the red line including co-variate Control – Medium*Time(Month) indicate co-variates significantly associated with weight change.*

Supplementary Table 1. Test of linear hypothesis of linear mixed-effect models of weight change according to age categories.

Test of linear hypotheses[a]			
Young adults (≤25 years) - Tested hypotheses[b,c,d]	**Estimates**[e]	**$p_{corrected}$**	**N total patients:** 102 **N total observations :**1305
Control High vs. average Switch High-to-Low and -Medium/High[b]	1.21	0.98	
Control Medium vs. average Switch Medium-to-Low and -Medium[b]	0.89	**<0.001**	
Control Low vs. Switch Low-to-Low[b]	0.41	0.60	
Switch High-to-High vs. average Switch High-to-Medium and Low[c]	1.83	0.46	
Switch Medium-to-Medium vs. Switch Medium-to-Low[c]	-0.33	0.26	
Switch High-to-Medium vs. Switch High-to-Low[d]	1.31	**<0.001**	
Adults (>25 years & <65 years) - Tested hypotheses[b,c,d]	**Estimates**	**$p_{corrected}$**	**N total patients:** 260 **N total observations:** 2903
Control High vs. average Switch High-to-Low and Medium/High[b]	-0.64	0.99	
Control Medium vs. average Switch Medium-to-Low and Medium[b]	0.24	**0.029**	
Control Low vs. Switch Low-to-Low[b]	0.54	**<0.001**	
Switch High-to-High vs. average Switch High-to-Medium and Low[c]	0.44	0.14	
Switch Medium-to-Medium vs. Switch Medium-to-Low[c]	0.25	0.45	
Switch High-to-Medium vs. Switch High-to-Low[d]	0.21	0.72	
Elderly (≥65 years) - Tested hypotheses[b,c,d,f]	**Estimates**	**$p_{corrected}$**	**N total patients:** 68 **N total observations:** 1107
Control High vs. average Switch High-to-Low and -Medium/High[b]	4.9	0.23	
Control Medium vs. average Switch Medium-to-Low and -Medium[b]	-0.14	0.96	
Control Low vs. Switch Low-to-Low[b]	-3.17	**<0.001**	
Switch Medium-to-Medium vs. Switch Medium-to-Low[c]	1.32	**0.003**	
Switch High-to-Medium vs. Switch High-to-Low[d]	-0.99	0.99	

[a]Interactions of time with both switch and control categories using the matrix of contrasts corrected for multiple testing. Median ages were 21, 42 and 76 years in the young adults, adults and elderly groups, respectively.

[b]Hypothesis: weight change over time of controls equals weight change over time of patients switching from a molecule within the same risk category of controls, after switch.

[c]Hypothesis: after switch, mean weight change over time of patients switching within the same category of risk equals weight change over time of patients switching to a lower-risk molecule.

[d]Hypothesis: after switch, mean weight change over time of patients switching high-to-low equals

weight change over time of patients switching high-to-medium.
[e]Young adult and adult controls taking medium risk drugs gained + 0.89% and +0.24 more weight for each additional month than patients switching from a medium-risk drug, respectively.
[f]No patients in the elderly category switched high-to-high.
Abbreviations: p: p-value (significant values in bold).

Supplementary Table 2. Test of linear hypothesis of linear mixed-effect models of weight change according to sex.

Test of linear hypotheses[a]			
Men - Tested hypotheses[b,c,d]	**Estimates**[e]	**$p_{corrected}$**	**N total patients:** 212 **N total observations :**2553
Control High vs. average Switch High-to-Low and -Medium/High[b]	1.03	0.091	
Control Medium vs. average Switch Medium-to-Low and -Medium[b]	0.45	**<0.001**	
Control Low vs. Switch Low-to-Low[b]	-0.035	1	
Switch High-to-High vs. average Switch High-to-Medium and -Low[c]	1.62	0.65	
Switch Medium-to-Medium vs. Switch Medium-to-Low[c]	-0.10	0.98	
Switch High-to-Medium vs. Switch High-to-Low[d]	0.40	**0.006**	
Women - Tested hypotheses[b,c,d]	**Estimates**	**$p_{corrected}$**	**N total patients:** 212 **N total observations:** 2673
Control High vs. average Switch High-to-Low and -Medium/High[b]	1.40	**<0.001**	
Control Medium vs. average Switch Medium-to-Low and -Medium[b]	0.48	**<0.001**	
Control Low vs. Switch Low-to-Low[b]	0.92	**<0.001**	
Switch High-to-High vs. average Switch High-to-Medium and -Low[c]	0.76	**0.001**	
Switch Medium-to-Medium vs. Switch Medium-to-Low[c]	-0.017	1	
Switch High-to-Medium vs. Switch High-to-Low[d]	0.46	**0.049**	

[a]Interactions of time with both switch and control categories using the matrix of contrasts corrected for multiple testing.
[b]Hypothesis: weight change over time of controls equals weight change over time of patients switching from a molecule within the same risk category of controls, after switch.
[c]Hypothesis: after switch, mean weight change over time of patients switching within the same category of risk equals weight change over time of patients switching to a lower-risk molecule.
[d]Hypothesis: after switch, mean weight change over time of patients switching high-to-low equals weight change over time of patients switching high-to-medium.
[e]Among men, controls taking medium risk drugs gained + 0.45% more weight for each additional month than patients switching from a medium-risk drug, and patients switching high-to-medium gained 0.40% more weight per month than patients switching high-to-low.
Abbreviations: p: p-value (significant values in bold).

Supplementary Table 3. Linear mixed-effect models results for polygenic risk scores for BMI or for BMI and psychiatric disorders**.**

Model 1[a] Polygenic risk score (BMI, general population[1])			**Model 2[a,b] Polygenic risk score (BMI, general population[2])**			**Model 3 [a] Polygenic risk score (BMI and schizophrenia[3])**			**Model 4 [a] Polygenic risk score (BMI and bipolar disorder[3])**			**Model 5 [a] Polygenic risk score (BMI and major depression[3])**		
E	CI	p	E	CI	p	E	CI	p	E	CI	p	E	CI	p
-1.14	-3.20 – 0.93	0.3	-0.06	-0.18 – 0.05	0.3	0.07	-0.07 – 0.21	0.3	0.07	-0.18 – 0.32	0.6	0.03	-0.13 – 0.20	0.7
$N_{patients}$: 241[c] $N_{observations}$: 3137														
-0.43	-2.55 – 1.70	0.7	-0.03	-0.14 – 0.09	0.7	0.04	-0.10 – 0.18	0.6	0.05	-0.22 – 0.31	0.7	-0.05	-0.23 – 0.12	0.5
$N_{patients}$: 241[d] $N_{observations}$: 2332														
-1.81	-6.04 – 2.43	0.4	-0.09	-0.30 – 0.13	0.4	0.08	-0.18 – 0.34	0.5	0.14	-0.40 – 0.68	0.6	0.14	-0.19 – 0.47	0.4
$N_{patients}$: 93[e] $N_{observations}$: 801														

[1,2,3] See Supplementary References

[a]Models included only Psymetab genotyped participants of European ancestry.

[b]A sensitivity analysis was performed including a PRS constructed with the 10 SNPs most associated with BMI or with the highest beta from the GWAS study of Locke et al., with no difference in the results (data not shown).

[c]Linear mixed-effect model also adjusted by sex, age at baseline, medical environment, baseline weight, five principal components and by the interaction of both switch and control categories with time. Models included controls and switch patients (observations before and after the switch).

[d]Linear mixed-effect model also adjusted by sex, age at baseline, medical environment, baseline weight, five principal components and time. Models included switch patients (observations before the switch) and controls.

[e]Linear mixed-effect model also adjusted by sex, age at baseline, medical environment, weight at the moment of the switch, five principal components and time. Models included switch patients (observations after the switch).

Abbreviations: E: Estimates; CI: 95% confidence interval; p: p-value; N: number.

Supplementary Table 4. Linear mixed-effect models of metabolic outcomes.

	Glucose[c]		Total cholesterol[d]		LDL cholesterol[d]		HDL cholesterol[d]		Triglycerides[c]		Systolic pressure		Diastolic pressure[e]	
Predictors [a,b]	E	p	E	p	E	P	E	p	E	p	E	p	E	p
Time (Month)	0.01	**0.047**	0.02	**0.001**	0.01	**0.005**	-0.00	0.098	0.02	**0.001**	0.04	0.51	0.21	0.12
Control Medium	-0.11	0.30	-0.08	0.55	-0.08	0.52	0.00	0.92	0.02	0.87	-1.31	0.43	0.78	0.57
Control Low	-0.17	0.29	-0.10	0.58	-0.05	0.77	0.02	0.80	-0.13	0.37	-3.73	0.083	-0.66	0.72
High-to-Medium	0.01	0.94	-0.22	0.061	-0.16	0.11	0.00	0.95	-0.14	0.24	-1.26	0.55	0.62	0.79
High-to-Low	-0.10	0.51	-0.27	**0.043**	-0.13	0.28	0.02	0.76	-0.25	0.080	1.81	0.37	1.76	0.52
Medium-to-Low	-0.23	0.10	-0.29	0.055	-0.26	0.053	-0.00	0.97	-0.12	0.36	1.82	0.35	1.63	0.41
High-to-High	0.30	0.41	-0.21	0.53	-0.04	0.88	-0.15	0.22	-0.01	0.98	-2.73	0.38	-8.80	0.17
Medium-to-Medium	-0.33	0.069	0.07	0.71	0.00	0.98	0.03	0.69	0.10	0.54	-1.44	0.52	2.31	0.28
Low-to-Low	-0.44	**0.032**	-0.30	0.17	-0.18	0.35	0.02	0.80	-0.28	0.15	-5.50	**0.034**	-1.77	0.50
N total patients	329		337		333		336		331		362		362	
N total observations	822		947		906		944		879		1996		1996	

[a]Linear mixed-effect model over two-year follow-up on glucose, total, LDL, HDL cholesterol, triglycerides, systolic and diastolic blood pressure adjusted by sex, age, baseline BMI and both switch and control groups. Glucose, total, LDL, HDL cholesterol and triglycerides are expressed in mmol/l. Blood pressure is expressed in mmHg.

[b]Reference group is High-risk control.

[c]Only fasting observation included.

[d]Adjusted by fasting status.

[e]Adjusted by both switch and control group interaction with time.

Abbreviations: N: number; E: estimates; p: p-value (significant values in bold).

Supplementary References

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