

Supplementary Material

A Marked Low-grade Inflammation and a Significant Deterioration in Metabolic Status in First Episode Schizophrenia: a Five-Year Follow-up Study

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Table S1. Serum mean levels, standard deviations (SD), and range of inflammatory and metabolic protein biomarkers (pg/ml), acylcarnitines, hexoses, body mass index, and waist circumference for control subjects (CSs, n = 58), first-episode psychosis (FEP) patients at baseline (before treatment with antipsychotics, FEP_b, n = 54), after 0.6-year treatment (FEP_{0.6-year}, n = 47), and after 5.1-year treatment (FEP_{5.1-year}, n = 38) with antipsychotics. In comparison between reduced and unrestricted models, p-values have been multiple tests corrected according to the false discovery rate (FDR) method. The unrestricted regression model is designated as True (i.e. more complex set of predictor variables explained more effectively biomarker level alterations over time) or False (i.e. unrestricted model did not provide more explanatory power than a simple one).

Regression equations for estimating biomarker level or biomarkers ratio alterations.	
Reduced model	$\log(\text{biomarker}) \sim \text{Age} + \text{Gender} + \text{Smoking} + (1 \text{Patient})$
Unrestricted model	$\log(\text{biomarker}) \sim \text{Age} + \text{Gender} + \text{Smoking} + \text{Visit} + \text{Time difference} + (1 \text{Patient})$

Visit = biomarker measurements at three-time points in the patients' group, Time1 = time difference between FEP_b and FEP_{0.6-year}, Time2 = time difference between FEP_{0.6-year} and FEP_{5.1-year}, (1 | Patient) = random effects of patients.

	CSs Mean ± SD Median (range)	FEP _b Mean ± SD Median (range)	FEP _(0.6-year) Mean ± SD Median (range)	FEP _(5.1-year) Mean ± SD Median (range)	Comparison between models	
					Adjusted p-value	True (T) or false (F)
Body mass index (BMI), waist circumference						
BMI	22.6 ± 2.78 22.6 (16.8 – 28.9)	22.8 ± 3.00 22.2 (18.4 – 30.2)	25.3 ± 3.94 24.4 (18.8 – 34.7)	27.8 ± 4.71 27.5 (18.8 – 43.0)	6×10^{-12}	T
Waist circumference	77.9 ± 12.6 77.0 (61.0 – 108)	81.0 ± 9.89 79.5 (64.0 – 110)	86.3 ± 11.2 86.0 (68.0 – 114)	94.4 ± 11.2 96.5 (65.0 – 118)	6×10^{-11}	T

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	CSs Mean ± SD Median (range)	FEP _b Mean ± SD Median (range)	FEP _(0.6-year) Mean ± SD Median (range)	FEP _(5.1-year) Mean ± SD Median (range)	Comparison between models	
					Adjusted <i>p</i> -value	True (T) or false (F)
Inflammatory biomarkers						
Interleukin (IL)-2	2.27 ± 1.26 2.50 (0.66 – 6.28)	3.15 ± 0.87 3.06 (1.18 – 6.69)	2.39 ± 1.14 2.10 (1.14 – 7.90)	3.52 ± 1.33 3.60 (0.72 – 8.27)	5 × 10 ⁻⁷	T
IL-4	1.33 ± 0.51 1.26 (0.79 – 3.71)	1.87 ± 0.57 1.79 (1.02 – 3.75)	1.62 ± 0.63 1.41 (0.92 – 4.32)	2.21 ± 0.56 2.24 (0.82 – 3.47)	3 × 10 ⁻⁹	T
IL-6	0.76 ± 0.59 0.59 (0.15 – 2.91)	1.27 ± 1.14 0.87 (0.33 – 5.03)	0.93 ± 0.76 0.72 (0.19 – 4.16)	1.12 ± 0.74 0.90 (0.52 – 4.45)	6 × 10 ⁻⁴	T
IL-8	5.98 ± 2.90 5.61 (1.61 – 13.8)	6.58 ± 4.07 5.59 (1.72 – 17.9)	5.66 ± 3.88 4.30 (1.25 – 17.4)	7.05 ± 3.05 6.59 (2.63 – 14.1)	4 × 10 ⁻⁴	T
IL-10	0.71 ± 0.42 0.59 (0.19 – 2.11)	0.73 ± 0.37 0.73 (0.19 – 1.65)	0.75 ± 0.49 0.65 (0.27 – 2.29)	1.44 ± 0.93 1.13 (0.50 – 4.94)	4 × 10 ⁻⁷	T
IL-1α	0.19 ± 0.13 0.14 (0.060 – 0.61)	0.29 ± 0.23 0.23 (0.060 – 1.33)	0.23 ± 0.19 0.17 (0.07 – 1.26)	0.30 ± 0.11 0.31 (0.060 – 0.58)	2 × 10 ⁻⁴	T
IL-1β	1.63 ± 0.91 1.48 (0.45 – 4.47)	1.41 ± 0.66 1.37 (0.44 – 3.44)	1.37 ± 0.76 1.39 (0.39 – 3.39)	1.60 ± 0.47 1.66 (0.46 – 2.23)	1 × 10 ⁻¹	F
Interferon gamma (IFN-γ)	0.30 ± 0.090 0.27 (0.19 – 0.55)	0.36 ± 0.14 0.36 (0.19 – 0.92)	0.27 ± 0.12 0.22 (0.17 – 0.69)	0.44 ± 0.21 0.38 (0.16 – 1.14)	3 × 10 ⁻⁸	T
Tumor necrosis factor alpha (TNF-α)	2.22 ± 1.40 1.86 (0.86 – 8.70)	1.98 ± 0.84 1.83 (0.97 – 5.76)	1.91 ± 0.59 1.79 (1.03 – 3.59)	2.39 ± 0.79 2.32 (0.90 – 4.61)	3 × 10 ⁻³	T
Monocyte chemoattractant protein-1 (MCP-1)	131 ± 76.7 115 (23.1 – 365)	127 ± 77.4 111 (21.2 – 381)	135 ± 80.2 116 (10.6 – 344)	170 ± 72.1 159 (36.5 – 353)	4 × 10 ⁻³	T
Ferritin	43.6 ± 55.2 21.4 (1.22 – 255)	90.0 ± 82.5 62.0 (4.26 – 386)	64.3 ± 75.8 32.5 (5.09 – 342)	92.7 ± 77.8 77.4 (3.35 – 269)	3 × 10 ⁻³	T
Metabolic biomarkers						
Resistin	2.53 ± 0.57 2.51 (0.88 – 4.10)	3.15 ± 1.33 2.85 (0.75 – 8.58)	2.78 ± 0.88 2.73 (1.42 – 5.63)	2.18 ± 1.01 1.90 (1.13 – 6.40)	1 × 10 ⁻⁴	T
Insulin	15.6 ± 14.3 9.02 (1.80 – 67.6)	12.9 ± 14.8 7.24 (1.54 – 64.4)	18.3 ± 16.0 12.3 (2.41 – 66.8)	8.28 ± 6.59 7.30 (1.90 – 35.6)	2 × 10 ⁻²	F
Leptin	2.07 ± 2.18 1.34 (0.38 – 12.8)	1.40 ± 1.69 0.87 (0.000 – 10.4)	2.59 ± 2.77 1.31 (0.000 – 12.5)	3.29 ± 3.90 1.39 (0.45 – 15.5)	1 × 10 ⁻⁴	T
Plasminogen activator inhibitor-1 (PAI-1)	21.9 ± 9.56 20.5 (6.33 – 49.9)	29.7 ± 13.6 26.5 (2.13 – 61.7)	25.8 ± 14.9 20.9 (4.81 – 73.0)	20.4 ± 12.8 18.1 (0.95 – 63.2)	2 × 10 ⁻⁴	T

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	CSs Mean ± SD Median (range)	FEP _b Mean ± SD Median (range)	FEP _(0.6-year) Mean ± SD Median (range)	FEP _(5.1-year) Mean ± SD Median (range)	Comparison between models	
					Adjusted <i>p</i> -value	True (T) or false (F)
Acylcarnitines						
C0	32.0 ± 7.82 31.8 (16.6 – 51.8)	34.6 ± 7.40 34.4 (18.3 – 52.0)	34.0 ± 9.63 33.4 (15.8 – 58.4)	37.1 ± 10.3 34.2 (18.7 – 67.2)	8×10^{-1}	F
C16	0.082 ± 0.021 0.080 (0.035 – 0.13)	0.11 ± 0.032 0.11 (0.046 – 0.20)	0.092 ± 0.029 0.085 (0.041 – 0.20)	0.11 ± 0.040 0.10 (0.057 – 0.22)	1×10^{-5}	T
C16-OH	0.009 ± 0.013 0.009 (0.000 – 0.084)	0.017 ± 0.005 0.016 (0.009 – 0.027)	0.019 ± 0.028 0.015 (0.008 – 0.20)	0.053 ± 0.099 0.022 (0.000 – 0.50)	3×10^{-2}	F
C16:1	0.026 ± 0.008 0.025 (0.015 – 0.071)	0.036 ± 0.012 0.036 (0.015 – 0.064)	0.028 ± 0.012 0.023 (0.011 – 0.062)	0.039 ± 0.022 0.032 (0.018 – 0.11)	4×10^{-5}	T
C16:1-OH	0.007 ± 0.013 0.008 (0.000 – 0.10)	0.014 ± 0.004 0.013 (0.007 – 0.028)	0.014 ± 0.012 0.011 (0.006 – 0.092)	0.034 ± 0.054 0.018 (0.000 – 0.24)	1×10^{-2}	F
C16:2	0.014 ± 0.007 0.012 (0.008 – 0.048)	0.015 ± 0.004 0.014 (0.008 – 0.027)	0.013 ± 0.005 0.013 (0.006 – 0.027)	0.026 ± 0.025 0.019 (0.008 – 0.11)	2×10^{-5}	T
C16:2-OH	0.016 ± 0.015 0.021 (0.000 – 0.045)	0.027 ± 0.005 0.027 (0.018 – 0.038)	0.029 ± 0.009 0.028 (0.019 – 0.075)	0.027 ± 0.018 0.024 (0.000 – 0.085)	2×10^{-3}	T
C18:0	0.039 ± 0.009 0.038 (0.022 – 0.073)	0.046 ± 0.013 0.046 (0.025 – 0.085)	0.042 ± 0.013 0.040 (0.022 – 0.074)	0.052 ± 0.021 0.043 (0.026 – 0.12)	3×10^{-3}	T
C18:1	0.096 ± 0.030 0.092 (0.058 – 0.18)	0.14 ± 0.046 0.14 (0.049 – 0.27)	0.096 ± 0.041 0.086 (0.039 – 0.27)	0.14 ± 0.048 0.13 (0.072 – 0.27)	8×10^{-8}	T
C18:1-OH	0.017 ± 0.018 0.015 (0.000 – 0.075)	0.028 ± 0.012 0.024 (0.013 – 0.053)	0.027 ± 0.016 0.017 (0.011 – 0.075)	0.031 ± 0.024 0.020 (0.000 – 0.10)	4×10^{-3}	T
C18:2	0.031 ± 0.009 0.029 (0.013 – 0.055)	0.042 ± 0.014 0.039 (0.020 – 0.081)	0.033 ± 0.015 0.030 (0.015 – 0.094)	0.047 ± 0.015 0.048 (0.025 – 0.093)	6×10^{-7}	T
C2	4.96 ± 1.68 4.90 (1.78 – 11.3)	4.65 ± 3.47 3.38 (0.51 – 14.0)	4.21 ± 1.70 3.95 (0.98 – 7.90)	6.97 ± 2.67 6.55 (3.16 – 13.2)	1×10^{-6}	T
C3	0.36 ± 0.11 0.36 (0.13 – 0.61)	0.25 ± 0.077 0.23 (0.14 – 0.49)	0.33 ± 0.13 0.30 (0.14 – 0.65)	0.54 ± 0.17 0.504 (0.28 – 1.00)	1×10^{-18}	T
C3-DC(C4-OH)	0.036 ± 0.023 0.043 (0.000 – 0.092)	0.062 ± 0.048 0.053 (0.025 – 0.32)	0.049 ± 0.017 0.045 (0.029 – 0.13)	0.050 ± 0.028 0.042 (0.000 – 0.12)	3×10^{-3}	T
C5-OH(C3-DC-M)	0.035 ± 0.032 0.049 (0.000 – 0.091)	0.060 ± 0.015 0.057 (0.036 – 0.11)	0.061 ± 0.015 0.059 (0.035 – 0.12)	0.062 ± 0.029 0.055 (0.000 – 0.15)	3×10^{-5}	T

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	CSs Mean ± SD Median (range)	FEP _b Mean ± SD Median (range)	FEP _(0.6-year) Mean ± SD Median (range)	FEP _(5.1-year) Mean ± SD Median (range)	Comparison between models	
					Adjusted <i>p</i> -value	True (T) or false (F)
Acylcarnitines						
C3-OH	0.028 ± 0.037 0.035 (0.000 – 0.25)	0.038 ± 0.010 0.040 (0.018 – 0.066)	0.043 ± 0.018 0.039 (0.023 – 0.14)	0.062 ± 0.060 0.044 (0.000 – 0.31)	2 × 10 ⁻²	F
C3:1	0.018 ± 0.017 0.026 (0.000 – 0.069)	0.030 ± 0.007 0.030 (0.018 – 0.048)	0.036 ± 0.035 0.031 (0.019 – 0.26)	0.042 ± 0.029 0.035 (0.000 – 0.12)	6 × 10 ⁻³	F
C4	0.22 ± 0.069 0.21 (0.12 – 0.42)	0.15 ± 0.043 0.15 (0.071 – 0.32)	0.17 ± 0.052 0.17 (0.077 – 0.31)	0.32 ± 0.11 0.31 (0.13 – 0.56)	1 × 10 ⁻¹⁵	T
C4:1	0.026 ± 0.025 0.036 (0.000 – 0.089)	0.046 ± 0.009 0.046 (0.027 – 0.061)	0.051 ± 0.033 0.045 (0.030 – 0.26)	0.064 ± 0.038 0.060 (0.000 – 0.16)	2 × 10 ⁻⁵	T
C5	0.17 ± 0.050 0.16 (0.000 – 0.32)	0.14 ± 0.042 0.14 (0.065 – 0.31)	0.17 ± 0.069 0.16 (0.075 – 0.39)	0.18 ± 0.067 0.18 (0.073 – 0.34)	4 × 10 ⁻⁴	T
C5-M-DC	0.023 ± 0.021 0.031 (0.000 – 0.074)	0.034 ± 0.011 0.037 (0.014 – 0.059)	0.036 ± 0.013 0.036 (0.010 – 0.089)	0.030 ± 0.022 0.023 (0.000 – 0.10)	2 × 10 ⁻²	F
C5:1	0.044 ± 0.040 0.056 (0.000 – 0.12)	0.076 ± 0.017 0.075 (0.040 – 0.14)	0.074 ± 0.021 0.071 (0.043 – 0.17)	0.091 ± 0.057 0.078 (0.000 – 0.28)	5 × 10 ⁻⁴	T
C5:1-DC	0.015 ± 0.014 0.020 (0.000 – 0.053)	0.023 ± 0.006 0.025 (0.010 – 0.032)	0.024 ± 0.008 0.023 (0.010 – 0.053)	0.024 ± 0.017 0.019 (0.000 – 0.083)	1 × 10 ⁻²	F
Hexoses, ratios of acylcarnitines						
Hexoses	4144 ± 823 4094 (2780 – 6663)	4258 ± 750 4075 (2802 – 5918)	4287 ± 867 4264 (2760 – 7189)	4887 ± 1104 4711 (3086 – 7271)	1 × 10 ⁻³	T
(C16+C18)/C0	0.0040 ± 0.0013 0.0036 (0.0023 – 0.0092)	0.0049 ± 0.0016 0.0046 (0.0019 – 0.010)	0.0041 ± 0.0011 0.0037 (0.0025 – 0.0069)	0.0046 ± 0.0020 0.0041 (0.0020 – 0.010)	5 × 10 ⁻³	T
(C16+C18:1)/C2	0.043 ± 0.015 0.038 (0.023 – 0.092)	0.085 ± 0.082 0.063 (0.022 – 0.50)	0.054 ± 0.047 0.042 (0.018 – 0.28)	0.037 ± 0.009 0.034 (0.019 – 0.056)	5 × 10 ⁻¹⁰	T
(C2+C3+C4+C5)/C0	0.19 ± 0.091 0.18 (0.066 – 0.73)	0.16 ± 0.12 0.12 (0.024 – 0.55)	0.16 ± 0.086 0.16 (0.033 – 0.61)	0.22 ± 0.084 0.20 (0.11 – 0.44)	2 × 10 ⁻⁵	T

Table S2. Estimated effects of the complex set of predictor variables on serum concentrations of inflammatory and metabolic protein biomarkers, acylcarnitines, hexoses, body mass index and waist circumference between control subjects (CSs, n = 58), first-episode psychosis patients at baseline (before treatment with antipsychotics, FEP_b, n = 54), after 0.6-year treatment (FEP_{0.6-year}, n = 47), and after 5.1-year treatment (FEP_{5.1-year}, n = 38) with antipsychotics: results from linear mixed-effects model.

	Intercept	Age	Gender	Smoking status	Disease and Treatment Effect			Time-Diff1	Time-Diff2					
					FEP patients before treatment	FEP patients after 0.6-year treatment	FEP patients after 5.1-year treatment							
	Effects of Independent Variables on the Dependent Variable (F-Value, p-Value)													
	t-Value, p-Value													
Body mass index (BMI), waist circumference														
BMI	$F_{(1,110)} = 1798$, $p < 1 \times 10^{-4}$	$F_{(1,77)} = 2.83$, $p = 0.10$	$F_{(1,110)} = 0.41$, $p = 0.52$	$F_{(2,77)} = 0.39$, $p = 0.67$	$F_{(3,77)} = 26.88$, $p < 1 \times 10^{-4}$	$t_{(77)} = -0.13$, $p = 0.90$	$t_{(77)} = 3.59$, $p = 6 \times 10^{-4}$	$t_{(77)} = 4.63$, $p < 1 \times 10^{-4}$	$F_{(1,77)} = 1.29$, $p = 0.26$					
Waist circumference	$F_{(1,110)} = 5466$, $p < 1 \times 10^{-4}$	$F_{(1,77)} = 1.00$, $p = 0.32$	$F_{(1,110)} = 24.18$, $p < 1 \times 10^{-4}$	$F_{(2,77)} = 0.66$, $p = 0.52$	$F_{(3,77)} = 24.27$, $p < 1 \times 10^{-4}$	$t_{(77)} = 0.91$, $p = 0.36$	$t_{(77)} = 4.00$, $p = 1 \times 10^{-4}$	$t_{(77)} = 5.50$, $p < 1 \times 10^{-4}$	$F_{(1,77)} = 0.24$, $p = 0.62$					
Inflammatory biomarkers														
Interleukin (IL)-2	$F_{(1,109)} = 9.84$, $p = 2 \times 10^{-3}$	$F_{(1,73)} = 0.01$, $p = 0.92$	$F_{(1,109)} = 0.95$, $p = 0.33$	$F_{(2,73)} = 0.70$, $p = 0.50$	$F_{(3,73)} = 15.85$, $p < 1 \times 10^{-4}$	$t_{(73)} = 4.92$, $p < 1 \times 10^{-4}$	$t_{(73)} = 1.61$, $p = 0.11$	$t_{(73)} = 4.31$, $p = 1 \times 10^{-4}$	$F_{(1,73)} = 0.28$, $p = 0.60$					
IL-4	$F_{(1,109)} = 0.0007$, $p = 0.98$	$F_{(1,72)} = 0.12$, $p = 0.73$	$F_{(1,109)} = 3.68$, $p = 0.06$	$F_{(2,72)} = 0.53$, $p = 0.59$	$F_{(3,72)} = 19.80$, $p < 1 \times 10^{-4}$	$t_{(72)} = 5.95$, $p < 1 \times 10^{-4}$	$t_{(72)} = 3.43$, $p = 1 \times 10^{-3}$	$t_{(72)} = 6.52$, $p < 1 \times 10^{-4}$	$F_{(1,72)} = 0.004$, $p = 0.95$					
IL-6	$F_{(1,109)} = 2.51$, $p = 0.12$	$F_{(1,72)} = 0.33$, $p = 0.56$	$F_{(1,109)} = 0.19$, $p = 0.67$	$F_{(2,72)} = 3.83$, $p = 0.03$	$F_{(3,72)} = 7.53$, $p = 2 \times 10^{-4}$	$t_{(72)} = 4.22$, $p = 1 \times 10^{-4}$	$t_{(72)} = 2.19$, $p = 0.03$	$t_{(72)} = 3.80$, $p = 3 \times 10^{-4}$	$F_{(1,72)} = 0.15$, $p = 0.70$					
IL-8	$F_{(1,109)} = 60.06$, $p < 1 \times 10^{-4}$	$F_{(1,72)} = 3.83$, $p = 0.05$	$F_{(1,108)} = 0.93$, $p = 0.34$	$F_{(2,72)} = 0.68$, $p = 0.51$	$F_{(3,72)} = 2.70$, $p = 0.05$	$t_{(72)} = 0.65$, $p = 0.52$	$t_{(72)} = -0.51$, $p = 0.62$	$t_{(72)} = 1.59$, $p = 0.11$	$F_{(1,72)} = 13.00$, $p = 6 \times 10^{-4}$					

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	Intercept	Age	Gender	Smoking status	Disease and Treatment Effect			Time-Diff1	Time-Diff2					
					FEP patients before treatment	FEP patients after 0.6-year treatment	FEP patients after 5.1-year treatment							
	Effects of Independent Variables on the Dependent Variable (F -Value, p -Value)													
	t -Value, p -Value													
Inflammatory biomarkers														
IL-10	$F_{(1,109)} = 0.57, p = 0.45$	$F_{(1,73)} = 0.72, p = 0.40$	$F_{(1,109)} = 0.44, p = 0.51$	$F_{(2,73)} = 2.27, p = 0.11$	$F_{(3,73)} = 14.42, p < 1 \times 10^{-4}$			$F_{(1,73)} = 0.64, p = 0.43$	$F_{(1,73)} = 0.002, p = 0.96$					
IL-1A	$F_{(1,109)} = 41.84, p < 1 \times 10^{-4}$	$F_{(1,73)} = 0.01, p = 0.92$	$F_{(1,109)} = 0.06, p = 0.80$	$F_{(2,73)} = 1.31, p = 0.28$	$F_{(3,73)} = 9.21, p < 1 \times 10^{-4}$			$F_{(1,73)} = 0.008, p = 0.93$	$F_{(1,73)} = 0.33, p = 0.57$					
IL-1B	$F_{(1,108)} = 8.21, p = 5 \times 10^{-3}$	$F_{(1,72)} = 6.69, p = 0.01$	$F_{(1,108)} = 0.28, p = 0.59$	$F_{(2,72)} = 0.94, p = 0.40$	$F_{(3,72)} = 2.04, p = 0.12$			$F_{(1,72)} = 0.03, p = 0.86$	$F_{(1,72)} = 1.14, p = 0.29$					
Interferon gamma (IFN- γ)	$F_{(1,108)} = 53.20, p < 1 \times 10^{-4}$	$F_{(1,70)} = 0.19, p = 0.66$	$F_{(1,108)} = 0.49, p = 0.48$	$F_{(2,70)} = 2.26, p = 0.11$	$F_{(3,70)} = 14.34, p < 1 \times 10^{-4}$			$F_{(1,70)} = 0.47, p = 0.49$	$F_{(1,70)} = 3.87, p = 0.05$					
Tumor necrosis factor-alpha (TNF- α)	$F_{(1,109)} = 24.72, p < 1 \times 10^{-4}$	$F_{(1,72)} = 1.65, p = 0.20$	$F_{(1,109)} = 3.19, p = 0.08$	$F_{(2,72)} = 1.77, p = 0.18$	$F_{(3,72)} = 3.73, p = 0.01$			$F_{(1,72)} = 1.45, p = 0.23$	$F_{(1,72)} = 4.62, p = 0.03$					
Monocyte chemoattractant protein-1 (MCP-1)	$F_{(1,109)} = 318.9, p < 1 \times 10^{-4}$	$F_{(1,73)} = 5.95, p = 0.02$	$F_{(1,109)} = 1.44, p = 0.23$	$F_{(2,73)} = 1.48, p = 0.23$	$F_{(3,73)} = 4.03, p = 0.01$			$F_{(1,73)} = 0.0001, p = 0.99$	$F_{(1,73)} = 4.54, p = 0.04$					
Ferritin	$F_{(1,109)} = 86.73, p < 1 \times 10^{-4}$	$F_{(1,74)} = 4.75, p = 0.03$	$F_{(1,109)} = 76.03, p < 1 \times 10^{-4}$	$F_{(2,74)} = 0.20, p = 0.82$	$F_{(3,74)} = 6.07, p = 9 \times 10^{-4}$			$F_{(1,74)} = 0.92, p = 0.34$	$F_{(1,74)} = 0.39, p = 0.54$					

Continued.

	Intercept	Age	Gender	Smoking status	Disease and Treatment Effect			Time-Diff1	Time-Diff2					
					FEP patients before treatment	FEP patients after 0.6-year treatment	FEP patients after 5.1-year treatment							
	Effects of Independent Variables on the Dependent Variable (F-Value, p-Value)													
	t-Value, p-Value													
Metabolic biomarkers														
Resistin	$F_{(1,109)} = 32.53, p < 1 \times 10^{-4}$	$F_{(1,74)} = 0.17, p = 0.68$	$F_{(1,109)} = 0.04, p = 0.84$	$F_{(2,74)} = 0.25, p = 0.78$	$F_{(3,74)} = 8.96, p = 1 \times 10^{-4}$			$F_{(1,74)} = 0.10, p = 0.76$	$F_{(1,74)} = 0.54, p = 0.46$					
Insulin	$F_{(1,108)} = 60.79, p < 1 \times 10^{-4}$	$F_{(1,74)} = 1.03, p = 0.31$	$F_{(1,108)} = 0.18, p = 0.67$	$F_{(2,74)} = 0.98, p = 0.38$	$F_{(3,74)} = 4.12, p = 9 \times 10^{-3}$			$F_{(1,74)} = 0.52, p = 0.47$	$F_{(1,74)} = 1.29, p = 0.26$					
Leptin	$F_{(1,108)} = 0.47, p = 0.49$	$F_{(1,71)} = 0.94, p = 0.33$	$F_{(1,108)} = 34.62, p < 1 \times 10^{-4}$	$F_{(2,71)} = 0.67, p = 0.51$	$F_{(3,71)} = 9.11, p < 1 \times 10^{-4}$			$F_{(1,71)} = 0.27, p = 0.60$	$F_{(1,71)} = 0.93, p = 0.34$					
Plasminogen activator inhibitor-1 (PAI-1)	$F_{(1,109)} = 68.21, p < 1 \times 10^{-4}$	$F_{(1,73)} = 2.18, p = 0.14$	$F_{(1,109)} = 0.14, p = 0.71$	$F_{(2,73)} = 6.10, p = 4 \times 10^{-3}$	$F_{(3,74)} = 8.62, p = 1 \times 10^{-4}$			$F_{(1,73)} = 0.79, p = 0.38$	$F_{(1,73)} = 1.05, p = 0.31$					
Acylcarnitines														
C0	$F_{(1,109)} = 1008, p < 1 \times 10^{-4}$	$F_{(1,74)} = 0.71, p = 0.40$	$F_{(1,109)} = 17.05, p = 1 \times 10^{-4}$	$F_{(2,74)} = 0.02, p = 0.98$	$F_{(3,74)} = 0.66, p = 0.58$			$F_{(1,74)} = 0.03, p = 0.87$	$F_{(1,74)} = 0.09, p = 0.76$					
C16	$F_{(1,109)} = 381.8, p < 1 \times 10^{-4}$	$F_{(1,73)} = 2.09, p = 0.15$	$F_{(1,109)} = 3.71, p = 0.06$	$F_{(2,73)} = 2.75, p = 0.07$	$F_{(3,73)} = 10.42, p < 1 \times 10^{-4}$			$F_{(1,73)} = 1.55, p = 0.22$	$F_{(1,73)} = 1.32, p = 0.25$					
C16-OH	$F_{(1,109)} = 0.04, p = 0.85$	$F_{(1,74)} = 0.05, p = 0.82$	$F_{(1,109)} = 0.02, p = 0.89$	$F_{(2,74)} = 0.52, p = 0.59$	$F_{(3,74)} = 4.00, p = 0.01$			$F_{(1,74)} = 0.04, p = 0.84$	$F_{(1,74)} = 0.40, p = 0.53$					
C16:1	$F_{(1,91)} = 557.2, p < 1 \times 10^{-4}$	$F_{(1,71)} = 0.92, p = 0.34$	$F_{(1,91)} = 0.67, p = 0.41$	$F_{(2,71)} = 1.14, p = 0.33$	$F_{(3,71)} = 8.44, p = 1 \times 10^{-4}$			$F_{(1,71)} = 2.30, p = 0.13$	$F_{(1,71)} = 1.23, p = 0.27$					

Continued.

	Intercept	Age	Gender	Smoking status	Disease and Treatment Effect			Time-Diff1	Time-Diff2					
					FEP patients before treatment	FEP patients after 0.6-year treatment	FEP patients after 5.1-year treatment							
	Effects of Independent Variables on the Dependent Variable (F-Value, p-Value)													
	t-Value, p-Value													
Acylcarnitines														
C16:1-OH	$F_{(1,109)} = 0.02, p = 0.88$	$F_{(1,74)} = 0.36, p = 0.58$	$F_{(1,109)} = 0.08, p = 0.77$	$F_{(2,74)} = 0.20, p = 0.82$	$F_{(3,74)} = 4.67, p = 5 \times 10^{-3}$ $t_{(74)} = 1.13, p = 0.26$			$F_{(1,74)} = 0.02, p = 0.89$	$F_{(1,74)} = 0.32, p = 0.57$					
C16:2	$F_{(1,84)} = 535.1, p < 1 \times 10^{-4}$	$F_{(1,71)} = 0.20, p = 0.66$	$F_{(1,84)} = 0.13, p = 0.71$	$F_{(2,71)} = 0.47, p = 0.63$	$F_{(3,71)} = 9.31, p < 1 \times 10^{-4}$ $t_{(71)} = 1.20, p = 0.24$			$F_{(1,71)} = 1.78, p = 0.19$	$F_{(1,71)} = 0.69, p = 0.41$					
C16:2-OH	$F_{(1,109)} = 4.90, p = 0.03$	$F_{(1,74)} = 1.76, p = 0.19$	$F_{(1,109)} = 0.46, p = 0.50$	$F_{(2,74)} = 0.70, p = 0.50$	$F_{(3,74)} = 6.77, p = 4 \times 10^{-4}$ $t_{(74)} = 3.70, p = 4 \times 10^{-4}$			$F_{(1,74)} = 0.03, p = 0.87$	$F_{(1,74)} = 0.40, p = 0.53$					
C18	$F_{(1,103)} = 603.2, p < 1 \times 10^{-4}$	$F_{(1,74)} = 0.78, p = 0.38$	$F_{(1,103)} = 0.45, p = 0.50$	$F_{(2,74)} = 0.05, p = 0.95$	$F_{(3,74)} = 5.12, p = 3 \times 10^{-3}$ $t_{(74)} = 2.63, p = 0.01$			$F_{(1,74)} = 0.57, p = 0.45$	$F_{(1,74)} = 2.50, p = 0.12$					
C18:1	$F_{(1,89)} = 245.7, p < 1 \times 10^{-4}$	$F_{(1,72)} = 0.66, p = 0.42$	$F_{(1,89)} = 0.05, p = 0.82$	$F_{(2,72)} = 1.20, p = 0.31$	$F_{(3,72)} = 16.02, p < 1 \times 10^{-4}$ $t_{(72)} = 4.72, p < 1 \times 10^{-4}$			$F_{(1,72)} = 2.53, p = 0.12$	$F_{(1,72)} = 0.0005, p = 0.98$					
C18:1-OH	$F_{(1,109)} = 8.28, p = 5 \times 10^{-3}$	$F_{(1,74)} = 0.11, p = 0.74$	$F_{(1,109)} = 1.55, p = 0.22$	$F_{(2,74)} = 2.49, p = 0.09$	$F_{(3,74)} = 5.49, p = 2 \times 10^{-3}$ $t_{(74)} = 3.27, p = 2 \times 10^{-3}$			$F_{(1,74)} = 1.55, p = 0.22$	$F_{(1,74)} = 0.12, p = 0.73$					
C18:2	$F_{(1,99)} = 517.0, p < 1 \times 10^{-4}$	$F_{(1,72)} = 1.36, p = 0.25$	$F_{(1,99)} = 2.09, p = 0.15$	$F_{(2,72)} = 0.10, p = 0.91$	$F_{(3,72)} = 13.85, p < 1 \times 10^{-4}$ $t_{(72)} = 3.87, p = 2 \times 10^{-4}$			$F_{(1,72)} = 1.62, p = 0.21$	$F_{(1,72)} = 0.41, p = 0.52$					

Continued.

	Intercept	Age	Gender	Smoking status	Disease and Treatment Effect			Time-Diff1	Time-Diff2					
					FEP patients before treatment	FEP patients after 0.6-year treatment	FEP patients after 5.1-year treatment							
	Effects of Independent Variables on the Dependent Variable (F -Value, p -Value)													
	t -Value, p -Value													
Acylcarnitines														
C2	$F_{(1,109)} = 57.05, p < 1 \times 10^{-4}$	$F_{(1,73)} = 2.77, p = 0.10$	$F_{(1,109)} = 3.38, p = 0.07$	$F_{(2,73)} = 4.70, p = 0.01$	$F_{(3,73)} = 13.25, p < 1 \times 10^{-4}$			$F_{(1,73)} = 0.004, p = 0.95$	$F_{(1,73)} = 0.41, p = 0.52$					
C3	$F_{(1,109)} = 17.30, p = 1 \times 10^{-4}$	$F_{(1,73)} = 1.86, p = 0.18$	$F_{(1,109)} = 10.15, p = 2 \times 10^{-3}$	$F_{(2,73)} = 0.60, p = 0.55$	$F_{(3,73)} = 43.78, p < 1 \times 10^{-4}$			$F_{(1,73)} = 0.39, p = 0.53$	$F_{(1,73)} = 4.57, p = 0.04$					
C3-DC(C4-OH)	$F_{(1,109)} = 0.60, p = 0.44$	$F_{(1,74)} = 2.98, p = 0.09$	$F_{(1,109)} = 1.49, p = 0.22$	$F_{(2,74)} = 1.04, p = 0.36$	$F_{(3,74)} = 6.17, p = 8 \times 10^{-4}$			$F_{(1,74)} = 0.22, p = 0.64$	$F_{(1,74)} = 0.005, p = 0.94$					
C5-OH(C3-DC-M)	$F_{(1,109)} = 13.18, p = 4 \times 10^{-4}$	$F_{(1,74)} = 0.04, p = 0.83$	$F_{(1,109)} = 1.21, p = 0.27$	$F_{(2,74)} = 2.19, p = 0.12$	$F_{(3,74)} = 11.15, p < 1 \times 10^{-4}$			$F_{(1,74)} = 0.04, p = 0.84$	$F_{(1,74)} = 0.0002, p = 0.99$					
C3-OH	$F_{(1,109)} = 1.17, p = 0.28$	$F_{(1,74)} = 0.09, p = 0.77$	$F_{(1,109)} = 0.21, p = 0.65$	$F_{(2,74)} = 0.14, p = 0.87$	$F_{(3,74)} = 4.77, p = 4 \times 10^{-3}$			$F_{(1,74)} = 0.10, p = 0.75$	$F_{(1,74)} = 0.06, p = 0.81$					
C3:1	$F_{(1,109)} = 0.45, p = 0.50$	$F_{(1,74)} = 3.28, p = 0.07$	$F_{(1,109)} = 0.16, p = 0.69$	$F_{(2,74)} = 0.01, p = 0.99$	$F_{(3,74)} = 5.44, p = 2 \times 10^{-3}$			$F_{(1,74)} = 0.48, p = 0.49$	$F_{(1,74)} = 0.007, p = 0.93$					
C4	$F_{(1,109)} = 99.47, p < 1 \times 10^{-4}$	$F_{(1,73)} = 0.12, p = 0.72$	$F_{(1,109)} = 0.58, p = 0.45$	$F_{(2,73)} = 0.12, p = 0.88$	$F_{(3,73)} = 35.34, p < 1 \times 10^{-4}$			$F_{(1,73)} = 0.44, p = 0.51$	$F_{(1,73)} = 1.25, p = 0.27$					
C4:1	$F_{(1,109)} = 2.17, p = 0.14$	$F_{(1,74)} = 2.04, p = 0.16$	$F_{(1,109)} = 0.24, p = 0.62$	$F_{(2,74)} = 0.01, p = 0.99$	$F_{(3,74)} = 10.53, p < 1 \times 10^{-4}$			$F_{(1,74)} = 0.50, p = 0.48$	$F_{(1,74)} = 0.18, p = 0.67$					

Continued.

	Intercept	Age	Gender	Smoking status	Disease and Treatment Effect			Time-Diff1	Time-Diff2					
					FEP patients before treatment	FEP patients after 0.6-year treatment	FEP patients after 5.1-year treatment							
	Effects of Independent Variables on the Dependent Variable (F-Value, p-Value)													
	t-Value, p-Value													
Acylcarnitines														
C5	$F_{(1,109)} = 91.05, p < 1 \times 10^{-4}$	$F_{(1,74)} = 1.76, p = 0.19$	$F_{(1,109)} = 12.03, p = 8 \times 10^{-4}$	$F_{(2,74)} = 0.86, p = 0.43$	$F_{(3,74)} = 8.24, p = 1 \times 10^{-4}$			$F_{(1,74)} = 0.46, p = 0.50$	$F_{(1,74)} = 0.02, p = 0.89$					
C5-M-DC	$F_{(1,109)} = 4.36, p = 0.04$	$F_{(1,74)} = 0.99, p = 0.32$	$F_{(1,109)} = 0.02, p = 0.90$	$F_{(2,74)} = 1.18, p = 0.31$	$F_{(3,74)} = 3.69, p = 0.02$			$F_{(1,74)} = 1.46, p = 0.23$	$F_{(1,74)} = 0.16, p = 0.69$					
C5:1	$F_{(1,109)} = 0.75, p = 0.39$	$F_{(1,74)} = 2.49, p = 0.12$	$F_{(1,109)} = 0.18, p = 0.67$	$F_{(2,74)} = 0.001, p = 0.99$	$F_{(3,74)} = 8.11, p = 1 \times 10^{-4}$			$F_{(1,74)} = 0.11, p = 0.74$	$F_{(1,74)} = 0.18, p = 0.67$					
C5:1-DC	$F_{(1,109)} = 7.65, p = 7 \times 10^{-3}$	$F_{(1,74)} = 0.05, p = 0.82$	$F_{(1,109)} = 0.25, p = 0.62$	$F_{(2,74)} = 2.63, p = 0.08$	$F_{(3,74)} = 5.19, p = 3 \times 10^{-3}$			$F_{(1,74)} = 0.04, p = 0.83$	$F_{(1,74)} = 0.36, p = 0.55$					
Hexoses														
Hexoses	$F_{(1,109)} = 10690, p < 1 \times 10^{-4}$	$F_{(1,73)} = 0.43, p = 0.51$	$F_{(1,109)} = 5.81, p = 0.02$	$F_{(2,73)} = 0.35, p = 0.71$	$F_{(3,73)} = 4.44, p = 6 \times 10^{-3}$			$F_{(1,73)} = 5.33, p = 0.02$	$F_{(1,73)} = 2.58, p = 0.11$					
Ratios of acylcarnitines														
(C16+C18)/C0	$F_{(1,103)} = 1737, p < 1 \times 10^{-4}$	$F_{(1,73)} = 0.06, p = 0.81$	$F_{(1,103)} = 3.93, p = 0.05$	$F_{(2,73)} = 1.88, p = 0.16$	$F_{(3,73)} = 4.64, p = 5 \times 10^{-3}$			$F_{(1,73)} = 1.53, p = 0.22$	$F_{(1,73)} = 1.17, p = 0.28$					
(C16+C18:1)/C2	$F_{(1,89)} = 224.7, p < 1 \times 10^{-4}$	$F_{(1,71)} = 5.96, p = 0.02$	$F_{(1,89)} = 5.22, p = 0.02$	$F_{(2,71)} = 3.33, p = 0.04$	$F_{(3,71)} = 20.81, p < 1 \times 10^{-4}$			$F_{(1,71)} = 0.71, p = 0.40$	$F_{(1,71)} = 0.29, p = 0.59$					
(C2+C3+C4+C5)/C0	$F_{(1,108)} = 50.42, p < 1 \times 10^{-4}$	$F_{(1,68)} = 5.13, p = 0.03$	$F_{(1,108)} = 6.64, p = 0.01$	$F_{(2,68)} = 2.34, p = 0.10$	$F_{(3,68)} = 10.36, p < 1 \times 10^{-4}$			$F_{(1,68)} = 0.14, p = 0.71$	$F_{(1,68)} = 0.72, p = 0.40$					