

1 **Target lipidomics reveals associations between serum sphingolipids and**
2 **insulin sensitivity by the glucose clamp**

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56 **Abstract**

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58 **Background**

59 This study aimed to systematically investigate the associations between serum sphingolipids and insulin
60 sensitivity as well as insulin secretion. This study also aimed to reveal potential predictors for insulin
61 sensitivity or give perceptive insight into disease processes.

62 **Methods**

63 We conducted a lipidomics evaluation of molecularly distinct SPs in the serum of 86 consecutive
64 Chinese adults with or without obesity and diabetes using electrospray ionization mass spectrometry
65 coupled with liquid chromatography. The GIR30 was measured under steady conditions to assess
66 insulin sensitivity by the gold standard hyperinsulinemic-euglycemic clamp. We created the ROC
67 curves to detect the serum SMs diagnostic value and establish the diagnosis of insulin sensitivity.

68 **Results**

69 Differential correlation network analysis illustrated correlations amongst lipids, insulin sensitivity,
70 insulin secretion and other clinical indexes. Total and subspecies of serum SMs and
71 globotriaosylceramides (Gb3s) were positively related to GIR30, free FAs (FFA 16:1, FFA20:4), some
72 long chain GM3 and complex ceramide GluCers showed strong negative correlations with GIR30.
73 Notably, ROC curves showed that SM/Cer and SM d18:0/26:0 may be good serum lipid predictors of
74 diagnostic indicators of insulin sensitivity close to conventional clinical indexes such as 1/HOMA-IR
75 (all areas under the curve >0.80) based on GIR30 as standard diagnostic criteria.

76 **Conclusions**

77 These results provide novel associations between serum sphingolipid between insulin sensitivity
78 measured by the hyperinsulinemic-euglycemic clamp. We further identify two specific SPs that may
79 represent prognostic biomarkers for insulin sensitivity.

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82 **Key Words:** lipidomics, sphingolipids, insulin sensitivity, clamp, insulin secretion

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84 **Background**

85 SPs, including SMs, GM3s, ceramides, and gangliosides, are a group of ubiquitously produced lipids
86 that play crucial roles in cell membrane function and cell signaling pathways(1). Sphingolipids and
87 their substrates and constituents, FAs, have been implicated in the pathogenesis of various metabolic
88 diseases associated with decreased insulin sensitivity/IR, obesity, diabetes, and atherosclerosis(2,3).
89 When β cells of obese and IR individuals fail to secrete enough insulin to compensate for decreased
90 insulin sensitivity, hyperglycemia develops(4). It is likely that perturbations in serum SPs and FAs are
91 associated with diseases. Identifying these associations may reveal useful predictors or give perceptive
92 insight into disease processes. For instance, decreased circulating saturated FAs through food intake, a
93 kind of harmful FAs, could improve mouse insulin sensitivity(5). Cell membrane GM3s were found to
94 display opposite associations with insulin resistance depending on acyl chain compositions(6). Based
95 on a study of 2302 Singapore Chinese population, two specific SPs might represent prognostic
96 biomarkers for T2DM (7). Another study found that SMs C14:0, C22:3, and C24:4 were positively
97 associated with insulin secretion and glucose tolerance(8). However, due to the complexity and
98 diversity of lipids, and differences in the analytical approaches adopted for sphingolipid measurements,
99 the precise associations of sphingolipids with clinical indices of insulin sensitivity and secretion remain
100 unclear. Fortunately, given the fundamentally development of LC-MS, the overall classification of lipid
101 species in biological processes and has been improved in recent years. Such advances have expanded
102 the collection of the “sphingolipidome” to more than 600 structurally distinct SPs and potentially
103 thousands of theoretical metabolites that are likely to exist(9). In our study, we used a profile with more
104 comprehensive coverage of different SP subclasses to recover their novel correlations with insulin
105 sensitivity.

106
107 Commonly used clinical indexes for the evaluation of insulin sensitivity/resistance, such as the HOMA-
108 IR, Matsuda index and QUICKI, are derived from circulating glucose and insulin levels, which are
109 simple and noninvasive but indirect and subject to fluctuation (10). The gold standard for assessing
110 insulin sensitivity is the hyperinsulinemic-euglycemic clamp developed by the DeFronzo group in the
111 1970s (11). This approach assesses insulin-mediated glucose utilization under steady-state conditions,

112 which is both laborious and time-consuming as well as limited for large-scale use. However, the
113 advantages of the glucose clamp are obvious for measuring insulin sensitivity/resistance directly and
114 straightforwardly and further distinguishing hepatic and peripheral insulin sensitivity/resistance
115 simultaneously when radiolabeled glucose tracers are used. To date, the glucose clamp has been applied
116 as a standard assessment for other clinical indexes in various cross-sectional studies and prospective
117 investigations to test the effect of different interventions on insulin sensitivity (12-14). Moreover, the
118 IVGTT is an alternative method recommended to test insulin secretion and evaluate pancreatic islet
119 function. It is acknowledged that a reduction in FPIR is the earliest detectable defect in β -cell function
120 in individuals predisposed to develop T2DM and that this defect largely indicates β -cell exhaustion
121 after years of compensation for antecedent IR (15).

122
123 SP metabolism is dysregulated in metabolic diseases and any of these specific lipid molecules may
124 represent a potential biomarker of insulin resistance or other metabolic diseases. To date, there have
125 been few systematic evaluations of the correlations between individual serum SP species with insulin
126 sensitivity assessed by the hyperinsulinemic-euglycemic clamp. In this study, we investigated the
127 associations of various serum SPs and FAs quantitated using a targeted lipidomic approach with insulin
128 sensitivity and insulin secretion(Figure 1). We aimed to 1) investigate the incipient SPs and FAs patterns
129 related to insulin sensitivity and insulin secretion, 2) identify predictive and diagnostic serum lipid
130 indicators related to insulin sensitivity or islet function, thus preventing elevated risks of related
131 symptoms and associated treatment expenditures, and. 3) explore and discuss potential lipid metabolic
132 pathways associated with insulin sensitivity or islet function.

133

134

135 **Materials and Methods**

136 **Study participants.** Briefly, 86 participants aged from 18 to 60 years (number of Female:46) were
137 enrolled in this project in Nanjing, Jiangsu Province, China. To broadly detect the range of insulin
138 sensitivity, participants were normal weight (n=25), overweight(n=9; $24 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$) or
139 obese(n=52($\text{BMI} > 30 \text{ kg/m}^2$)), and with or without diabetes(number of participants with diabetes:25).

140 Exclusion criteria included use of medication or supplements, smoking or high alcohol use (>4 and >2
141 standard drinks/week for men and women, respectively), other major diseases or presence of acute
142 inflammation or pregnancy(Figure 2).

143

144 **Hyperinsulinemic-euglycemic clamp.** The hyperinsulinemic-euglycemic clamp presumes that the
145 hyperinsulinemic state induced by a high dose of insulin infusion ($>80 \text{ mU/m}^2 \cdot \text{min}$) is sufficient to
146 totally suppress hepatic glucose production and that there is no net change in the circulating blood
147 glucose concentration under steady conditions(Supplementary Figure 1). Therefore, the GIR is
148 equivalent to that of whole-body GDR or M value, which represents body insulin sensitivity(11). After
149 an overnight fast, subjects were studied the next morning in the supine position. A prepared dose of
150 insulin (80 mU/m^2) was injected over the next 10 minutes to achieve a steady-state insulin concentration.
151 The clamp duration was at least 2h. A variable infusion of 20% glucose was started to maintain the
152 plasma glucose concentration at 5 mmol/L (4.5-5.5 mmol/L). GIR_{30} was calculated from the mean
153 glucose infusion rate during the last 30 minutes (14).

154

155 **IVGTT.** Briefly, 0.3 g/kg body weight of a 20% glucose solution was given within 3 minutes. The
156 FPIR is defined as the initial burst of insulin, which is released within the first 10 minutes and peaks at
157 2-4 minutes after glucose injection. After the acute response, there is a second-phase insulin secretion,
158 which rises more gradually (16). Blood samples for the measurement of plasma glucose and serum
159 insulin were collected at 0, 2, 4, 6, 8, 10, 20, 30, and 60 minutes. The FPIR was calculated as the mean
160 of the 2- to 4-minute samples minus the mean pre-stimulus hormone concentration (0 minutes) (17).

161

162 **Laboratory measurements.** Blood glucose was analyzed by a blood glucose biochemical analyzer
163 (Germany, Biosen). Serum insulin and C-peptide were measured by chemiluminescent methods.
164 HbA1c was analyzed by a chromatographic technique, and TC, TG, LDL-c, HDL-c and other
165 biochemical phenotypes were measured with standard enzymatic assays in the laboratory of the First
166 Affiliated Hospital of Nanjing Medical University, Nanjing, China.

167

168 **Targeted lipidomics analysis.** Lipids were extracted from serum (20 μ L) using a modified Bligh and
169 Dyer's extraction procedure (double rounds of extraction) and dried in a SpeedVac under OH mode.
170 Prior to analysis, lipid extracts were resuspended in chloroform:methanol 1:1 (v/v) spiked with
171 appropriate internal standards. All lipidomic analyses were carried out on an Exion UPLC system
172 coupled with a QTRAP 6500 PLUS system (Sciex) as described previously(18). Sphingolipids were
173 separated on a Phenomenex Luna Silica 3 μ m column (i.d. 150x2.0 mm) under the following
174 chromatographic conditions: mobile phase A (chloroform:methanol:ammonium hydroxide, 89.5:10:0.5)
175 and mobile phase B (chloroform:methanol: ammonium hydroxide: water, 55:39:0.5:5.5) at a flow rate
176 of 270 μ L/min and column oven temperature at 25 $^{\circ}$ C. Individual sphingolipid species were quantified
177 by reference to spiked internal standards including Cer d18:1/17:0, GluCer d18:1/8:0, LacCer d18:1/8:0,
178 and SM d18:1/12:0, obtained from Avanti Polar Lipids; d₃-GM₃ d18:1/18:0 and Gb₃ d18:1/17:0
179 purchased from Matreya LLC; d₈-FFA 20:4 from Cayman Chemicals; and d₃₁-FFA16:0 from Sigma-
180 Aldrich.

181
182 **Statistical analysis.** Lipids were divided into groups and analyzed based on carbon atom and double
183 bond numbers. The typical cutoff value of GIR₃₀ (or GDR, M value) of 4.9-5.2 mg/kg per minute was
184 used to define insulin sensitive or resistant subjects(14,19). In our study, the cutoff point of GIR₃₀ was
185 set as 5.1 mg/(kg *min), which was also the median of consecutive 86 subjects. Differences in metabolic
186 characteristics between two groups divided by GIR₃₀ were calculated by t-test or the Mann-Whitney U
187 test. Analyses were performed using SPSS for Macintosh version 25.0 (SPSS Inc, Chicago, IL, USA).
188 Associations between metabolic parameters and lipid species were analyzed by Pearson correlation
189 based on univariate logistic regression and adjusted for multiple factors, including age, sex, BMI, HDL-
190 c, LDL-c, TG, TC, ALT and AST. Gephi was used to build correlation networks from differentially
191 correlated lipid pairs. Data are presented as the mean \pm SD or median (range). P<0.05 was considered
192 statistically significant.

193

194 **Results**

195 **Participants' characteristics.** Table 1 shows the characteristics of the 86 subjects in our study.
196 According to the glucose clamp results, all the participants were divided into insulin-resistant and
197 insulin-sensitive groups by GIR_{30} , which was defined as $5.1 \text{ mg}/(\text{kg} \cdot \text{min})$ (Table 1). We also applied
198 IVGTT to evaluate islet function, and all individuals were separated into high insulin secretion and low
199 insulin secretion groups by FPIR (Table 2). Subjects who presented insulin sensitivity were similar in
200 age and sex to IR individuals but had lower levels of serum fasting glucose and 2h-OGTT glucose,
201 neutral lipids including TC, TG, HDL-c, and LDL-c and liver enzymes including ALT and AST. Those
202 who showed lower FPIR had comparable age, BMI and neutral lipids but higher levels of serum fasting
203 glucose and 2h-OGTT glucose than those with high FPIR.

204
205 **Serum lipids and basic clinical characteristics** A. total of 90 lipid species in 7 classes of lipids,
206 including FFAs, SMs, ceramides, GluCers, LacCers, GM3s and Gb3s, were quantitated and analyzed
207 in the 86 human serum samples. We first evaluated differences among lipids with age and gender. There
208 was a tendency of increased SMs and significant enhancements in GluCer d18:0/18:0 and Gb3
209 d18:1/20:0 ($P < 0.05$) and decreases in GM3 d18:1/18:0, GM3 d18:0/18:0, and GM3 d18:1/20:0 ($P < 0.05$)
210 in females compared with males ($P < 0.05$); however, no differences were found in the total or subtypes
211 of serum ceramides (Supplementary Table 1). The lipid classes that extensively increased with age were
212 FFAs, ceramides and GM3 ($P < 0.05$), and those that tended to drop were SMs, GluCer and LacCer
213 (Supplementary Table 2). Similarly, in individuals with high BMI values, the perceivably increased
214 lipids were FFAs, ceramides and GM3s, while lipids such as SMs, GluCers and LacCers declined
215 (Supplementary Table 3).

216
217 **Differential analysis and correlation network of GIR and FPIR.** We used a heatmap to visualize the
218 trends of lipidomics among the 86 individuals divided by GIR_{30} (Figure 3, Supplementary Table 4). The
219 results showed a significant higher in total serum SMs in the high GIR_{30} (insulin sensitive) group
220 ($P < 0.05$) and a mild tendency of serum GluCers, LacCers and Gb3s, especially GluCer d18:1/20:0 and
221 Gb3 d18:1/24:0, to increase. However, in the high GIR_{30} group, a decrease was also seen in some FFAs,
222 ceramides and GM3s (Figure 3), especially C18 FFAs (FFA 18:3, FFA 18:1, FFA 18:0) and FFA16:1,

223 long-chain unsaturated ceramides (Cer d18:1/22:0, Cer d18:1/24:0, Cer d18:1/24:1) and most saturated
224 GM3s (GM3 d18:0/16:0, GM3 d18:1/18:0, GM3 d18:0/18:0, GM3 d18:1/20:0, GM3 d18:0/20:0, GM3
225 d18:1/22:0, GM3 d18:0/22:0, GM3 d18:0/24:0). Interestingly, most serum lipids increased in
226 individuals with low insulin secretion, including FFAs (FFA 22:6, FFA 22:5, FFA 18:2, FFA 18:1, FFA
227 18:0, FFA 16:0), Lac-Cers (LacCer d18:1/16:0, LacCer d18:1/18:0, LacCer d18:1/20:0, LacCer
228 d18:1/22:0, LacCer d18:1/24:0, LacCer d18:1/24:1), ceramide (Cer d18:1/22:0, Cer d18:1/24:0, Cer
229 d18:1/24:1), and GM3 (GM3 d18:0/16:0, GM3 d18:1/18:0, GM3 d18:0/20:0, GM3 d18:0/24:0, GM3
230 d18:1/22:0, GM3 d18:0/22:0, GM3 d18:1/24:0, GM3 d18:0/24:0) (Supplementary Table 5). These
231 findings might be because of lipid toxicity.

232 A correlation network was constructed to systematically evaluate the correlation of the clinical indexes
233 and lipidomics, as well as lipid-related interrelationships. We raised our correlation coefficient limit to
234 0.2 ($p < 0.05$), and the results indicated that the lipids that were positively related to GIR₃₀ including
235 GluCers (GluCer d18:1/20:0, GluCer d18:1/22:0, GluCer d18:0/24:0, GluCer d18:0/24:1), Gb3s (GB3
236 d18:1/24:0, GB3 d18:1/16:0) and all SMs (SM d18:1/19:1, SM d18:1/23:1, SM d18:1/25:1, SM
237 d18:1/25:0, SM d18:0/25:0, SM d18:1/26:1, SM d18:1/26:1, SM d18:0/26:0, and so on), while FFAs
238 (FFA16:1, FFA20:4) and GM3 (GM3 d18:1/18:0, GM3 d18:0/18:0, GM3 d18:1/20:0, GM3 d18:0/20:0)
239 were negatively correlated with GIR₃₀. This relationship still existed when adjusted for age, sex, BMI,
240 TG, TC, HDL-c, LDL-c, ALT and AST (Figure 4 Supplementary Table 6). Serum lipids showed a
241 negative relationship with FPIR, including FFAs (FFA22:5, FFA18:2, FFA18:1, FFA16:0), GluCers
242 (GluCer d18:1/16:0, GluCer d18:1/18:0, GluCer d18:1/20:0), LacCer (LacCer d18:1/20:0, LacCer
243 d18:1/24:0, LacCer d18:1/24:1), which still existed after adjustment for age, sex and BMI (Figure 4,
244 Supplementary Table 6). Notably, HDL is a lipid protein known to transport SMs. Our data showed
245 that HDL-c, not LDL-c, was correlated positively with most SMs.

246
247 **Use of the ROC test for the diagnosis of insulin sensitivity.** To discover serum lipid predictive and
248 prognostic biomarkers for insulin sensitivity evaluation, we assessed the predictive value of various
249 lipids by ROC curve analysis using GIR as a standard criterion (Figure 5, Supplementary Table 7).
250 Notably, the ratio of total serum SMs and ceramides (SM/Cer) showed high diagnostic efficiency, as it

251 was equal to 1/HOMA-IR, with 0.85 (0.77-0.94) and 0.85 (0.77-0.93), respectively. Moreover, SM
252 18:0/26:0, a subspecies of SMs, showed close and high diagnostic efficiency with 0.84 (0.75-0.93),
253 while other lipids showed lower diagnostic efficiency, such as total serum ceramides 0.35 (0.23-0.46)
254 and FFAs 0.38 (0.26-0.5).

255

256 **Discussion**

257 In the current work, we report the systematic analysis of the sphingolipidome, allowing for an accurate
258 evaluation of the associations between serum SPs content and obesity and diabetes related
259 characteristics, such as insulin sensitivity, BMI, blood lipids, and HOMA-IR. We also found that higher
260 concentration of serum free FAs(FFA 22:6, FFA 22:5, FFA 18:2, FFA 18:1), substrates and constituents
261 of SPs, were associated with a higher risk of decreased insulin secretion. Of note, ROC curves showed
262 that SM/Cer and SM d18:0/26:0 may be good serum lipid predictors of diagnostic indicators for insulin
263 sensitivity close to conventional clinical indexes such as 1/HOMA-IR (all areas under the curve >0.80)
264 based on GIR₃₀ as standard diagnostic criteria.

265

266 We conducted a lipidomics evaluation of molecularly distinct SPs in the serum of 86 consecutive
267 Chinese adults with or without obesity and diabetes using electrospray ionization mass spectrometry
268 coupled with liquid chromatography. Our study involved a thorough evaluation of lipid profile changes
269 in human serum samples among 90 lipid species. These lipids are from 7 subclasses, including FFAs
270 (15 species), SMs (27 species), ceramides (8 species), GluCers (12 species), LacCers (8 species), GM3s
271 (14 species) and Gb3s (6 species). We found an increasing tendency in complex serum sphingolipids
272 (SPs), including SMs and GluCers, in females, which is consistent with recent large-scale lipidomic
273 investigations of Chinese T2DM patients in Singapore (7). The possible reason for sex differences
274 might be sex hormone estrogens, which could improve sphingolipid synthesis and reduce sphingolipid
275 degradation by attenuating acid sphingomyelinase activities (20,21). We also observed that serum FFAs,
276 ceramides and GM3 were significantly higher in individuals of older age or with a higher BMI, which
277 might be due to the exacerbation of lipid-related inflammatory factors with age or BMI (7,22-24).

278 Interestingly, our results showed that SMs showed no significant changes with age or BMI, indicating
279 that SMs were less likely to be age- or BMI-related proinflammatory mediators.

280

281 The glucose infusion rate over 30 minutes (GIR_{30}) under steady conditions to assess insulin sensitivity
282 by the gold standard hyperinsulinemic-euglycemic clamp, and first-phase insulin release (FPIR) to
283 evaluate insulin secretion by the intravenous glucose tolerance test (IVGTT).

284 In comparison to previous studies (7,25,26), we further identified more lipid species related to obesity
285 and T2DM. In general, serum FFAs, ceramides and GM3s were decreased in subjects with high GIR_{30} ;
286 however, serum SMs, GluCers, LacCers and Gb3s were increased in individuals with high GIR_{30} .

287 Remarkably, all species of serum SMs analyzed were relevant to increased insulin sensitivity, while
288 partial species of serum ceramides (Cer d18:1/22:0, Cer d18:1/24:0, Cer d18:1/24:1) were corroborated
289 with a higher risk of impaired insulin sensitivity. In mammals, substrate specificity is distinguished

290 by CerS with N-acyl chain length. CerS has six isoforms (CerS1-6), and CerS2 seems to be a unique
291 enzyme with a higher activity for very long-chain fatty acids such as C22-C26. Our findings showed
292 that these very long-chain ceramides (Cer d18:1/22:0, Cer d18:1/24:0, Cer d18:1/24:1) were increased

293 in IR individuals, consistent with part of a previous study indicating that ceramides with larger carbon
294 atom numbers and more unsaturated bonds were more strongly associated with an increased risk of
295 diabetes (7). These findings suggested that compositional variations in specific species of ceramides

296 were associated with risks of IR or diabetes, even though the number of total ceramides remained
297 unchanged. We also found a positive correlation between serum GluCers and GIR_{30} , and the paradox
298 of correlations indicated that more complex ceramides are different from ceramide regulation. Cross-

299 sectional studies about serum SMs and insulin sensitivity in humans are limited. Among these studies,
300 the associations between SMs and HOMA-IR are still controversial (25,27-29). This discrepancy may
301 be attributed to a number of factors: 1) ethnic characteristics, 2) effective population size, 3) age span

302 changes from young adults to elderly individuals, 4) accuracy of clinical indicators such as HOMA-IR,
303 Matsuda index or QUICKI, 5) different lipidomics analytical platforms, 6) combined influence of body
304 weight, 7) onset of diabetes time course, 8) drug intervention for diabetes, and 9) accompaniment by

305 other metabolic diseases. Interestingly, our results were notable: all species of SMs showed a strong

306 positive relationship with GIR₃₀, and only some ceramides were negatively related to GIR₃₀. The
307 characteristics of the study were as follows: 1) young and middle-aged adults between 18 and 56
308 (median 26.5), 2) body weight ranging from normal weight to overweight to obese, 3) obese subjects
309 with or without newly diagnosed diabetes, 4) a thorough evaluation of SPs specific for 27 species of
310 SMs and 8 species of ceramides through targeted lipidomics measurements, and 5) insulin sensitivity
311 evaluated by the gold standard, glucose clamp evaluation.

312

313 We created the ROC curves to detect the serum SMs diagnostic value and establish the diagnosis of
314 insulin sensitivity based on GIR₃₀ derived from the glucose clamp, which is the standard method, and
315 the cutoff point of GIR₃₀ was set as 5.1 mg/(kg *min). ROC analysis provides tools to screen possibly
316 optimal models in a direct and natural way of diagnostic decision making. It is a comparison of two
317 operating characteristics as the criterion changes. In the current study, we found that serum very long-
318 chain SM d18:0/26:0 and the ratio of total serum SMs and Cers (SM/Cer) could be good predictors of
319 insulin sensitivity that were very close to 1/HOMA-IR. Although SM d18:0/26:0 accounted for the
320 lowest portion of total serum SMs, it seems to be a much more sensitive indicator of insulin sensitivity.
321 Ceramides are substrates that generate SMs and are intermediate lipid links in sphingolipid metabolism.
322 We used SM/Cer as a novel index that reflects the direction of sphingolipid reactions. As the ratio
323 increases, more SMs are produced in the forward direction. We aimed to discover the pathological
324 relevance of our identified lipids with regard to insulin sensitivity. Because sphingolipid synthesis and
325 catabolism are dysregulated in metabolic diseases, any of these specific molecules may reflect a
326 potential biomarker of decreased insulin sensitivity or other pathologies (30). A study also revealed that
327 a metabolite panel appreciably improved T2DM risk prediction over or close to conventional clinical
328 factors (18,31). The serum lipid parameters we identified could be good predictors compared with
329 HOMA-IR, where GIR₃₀ was used as a standard reference. These predictors we screened emphasized
330 that the scarce and uncommon lipids might be useful for further insulin sensitivity mechanism
331 exploration as well as clinical diagnosis and prevention.

332

333 We did not find specific lipid indicators of insulin secretion by ROC analysis. However, our correlation
334 network analysis data showed a negative association between serum total FFAs and FPIR, and it
335 disappeared after adjustment for age, sex, BMI, TC, TG, HDL-c, LDL-c, ALT and AST. More
336 interestingly, 18-chain FFAs and 22-chain FFAs remained negatively correlated with FPIR when
337 adjusted for the above factors, which indicated a strong relationship between these subtypes of FFAs
338 and FPIR. A previous study based on the OGTT observed an association between higher total fasting
339 plasma FFA levels and lower insulin secretion in children and adults without adjustments for
340 confounding factors (32). Some studies proved that chronic FFA-induced lipotoxicity on pancreatic
341 islets contributed to β cell dysfunction (33,34). Therefore, a reduction in elevated plasma FFA levels
342 might be a critical therapeutic target for obesity-related type 2 diabetes. Although some studies showed
343 that 24-72 h fatty acid stimulation increased insulin secretion in isolated islets from nondiabetic mice
344 or humans (35,36), there were two different notable effects of short-term and long-term FFA stimuli on
345 insulin secretion, and β cell function was impaired by long-term FFA stimulation. We considered that
346 the negative association between these subtypes of serum FFAs, including 18-chain and 22-chain FFAs
347 and FPIR in our study population, represented long-term damage to insulin secretion.

348
349 The major strengths of our current study are as follows. First, our targeted lipidomics approach
350 permitted the unambiguous identification and accurate quantitation of serum lipids. This procedure
351 unveiled unambiguous identification and accurate quantitation of serum lipids and evaluated systematic
352 lipid pathway coregulation via multiple correlation analyses. Second, in terms of the study cohorts, we
353 screened serum lipid predictors for the diagnosis of insulin sensitivity in Chinese individuals including
354 normal-weight, overweight, obese and diabetic subjects, which is the gold standard for evaluating
355 insulin sensitivity clinically. Third, we found that serum very long-chain SM (d18:0/26:0) and the
356 SM/Cer could be good predictors for insulin sensitivity, which was very close to 1/HOMA-IR and of
357 great value for diagnosis and prevention. However, there were also some limitations. First, lifestyle
358 habits, including diet and exercise, were not controlled in the current study due to the lack of formal
359 questionnaire or recording. These habits may also influence the analysis of lipids, since some
360 sphingolipid species were shown to increase in HFD-induced obese mice (37,38). Second, laborious

361 and time-consuming glucose clamps limited our cross-sectional study from being performed on a large
362 scale, and further work is required to verify our findings. Third, it might influence the serum
363 sphingolipid patterns that IR patients in our study had higher BMI than those of insulin sensitivity ,
364 since we corrected these effects through statistics methods.

365

366 **Conclusion**

367 In summary, these results provide novel associations between serum sphingolipid levels and insulin
368 sensitivity measured by hyperinsulinemic-euglycemic clamp. This finding suggests that the balance of
369 SMs metabolism, rather than ceramide, is correlated with the pathology of insulin resistance, obesity
370 and T2DM. We further identified two specific SPs that may represent prognostic biomarkers for insulin
371 sensitivity.

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380 **Abbreviations**

381 SP: sphingolipid; SM: sphingomyelin; GM3, sphingosine; FAs, fatty acids; GluCers: Glu-ceramides;
382 LacCers: Lac-ceramides; GIR₃₀: glucose infusion rate over 30 minutes; FPIR, first-phase insulin release;
383 IVGTT: intravenous glucose tolerance test; ROC: receiver operating characteristic; IR, insulin
384 resistance; LC-MS, liquid chromatography-mass spectrometry; QUICKI: quantitative insulin
385 sensitivity check index; GDR, glucose disposal; M: metabolizable glucose; TC: total cholesterol; TG:
386 triglyceride; LDL-c: LDL-cholesterol; HDL-c: HDL-cholesterol; ALT: alanine transaminase; AST:
387 aspartate transaminase; Gb3: globotriaosylceramides; CerS: ceramide synthase; SM/Cer: ratio of total
388 serum SMs and Cers.

389

390 **Ethics approval and consent to participate**

391 This study protocol was approved by the Institutional Review Board of the First Affiliated Hospital of
392 Nanjing Medical University, and all participants provided written informed consent (2014-SR-003). All
393 participants provided written informed consent prior to study entry.

394

395 **Consent for publication**

396 All authors have participated in the work and have reviewed and agree with the content of the article.

397

398 **Availability of data and materials**

399 We do not have governance permissions to share individual level data on which these analyses were
400 conducted since they derive from clinical record data. However, for any bona fide requests to audit the
401 validity of the analyses, the verifiable research pipeline which we operate means that one can request
402 to view the analyses being run and the same tabulations resulting. We are also happy to share summary
403 statistics for those wishing to conduct meta-analyses with other studies.

404

405 **Competing interests**

406 The authors declared that there is no conflict of interest associated with this article.

407

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413

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415 The authors thank the staff and participants for their important contributions. Jingya Ye, Xuan Ye and
416 Wanzi Jiang were responsible for data collection, analysis and writing of the first draft of manuscript.
417 Zhenzhen Fu and Yingyun Gong contributed to the human glucose clamp study performance and
418 guidance of clinical data acquisition. Jingya Ye, Xuan Ye, Wanzi Jiang, Xiaomei Geng, Chenxi Zhao,

419 Chenyan Lu, Yizhe Ma, and Panpan Yang took part in human glucose clamp performance. Sin Man
420 Lam and Guanghou Shui contributed to lipidomic measurement. John Zhong Li, Feng Chen and Tao
421 Yang contributed to data analysis and statistic process. Hongwen Zhou was the guarantors of this work
422 and, as such, had full access to all of the data in the study and take responsibility for the integrity of the
423 data and the accuracy of the data analysis.

424

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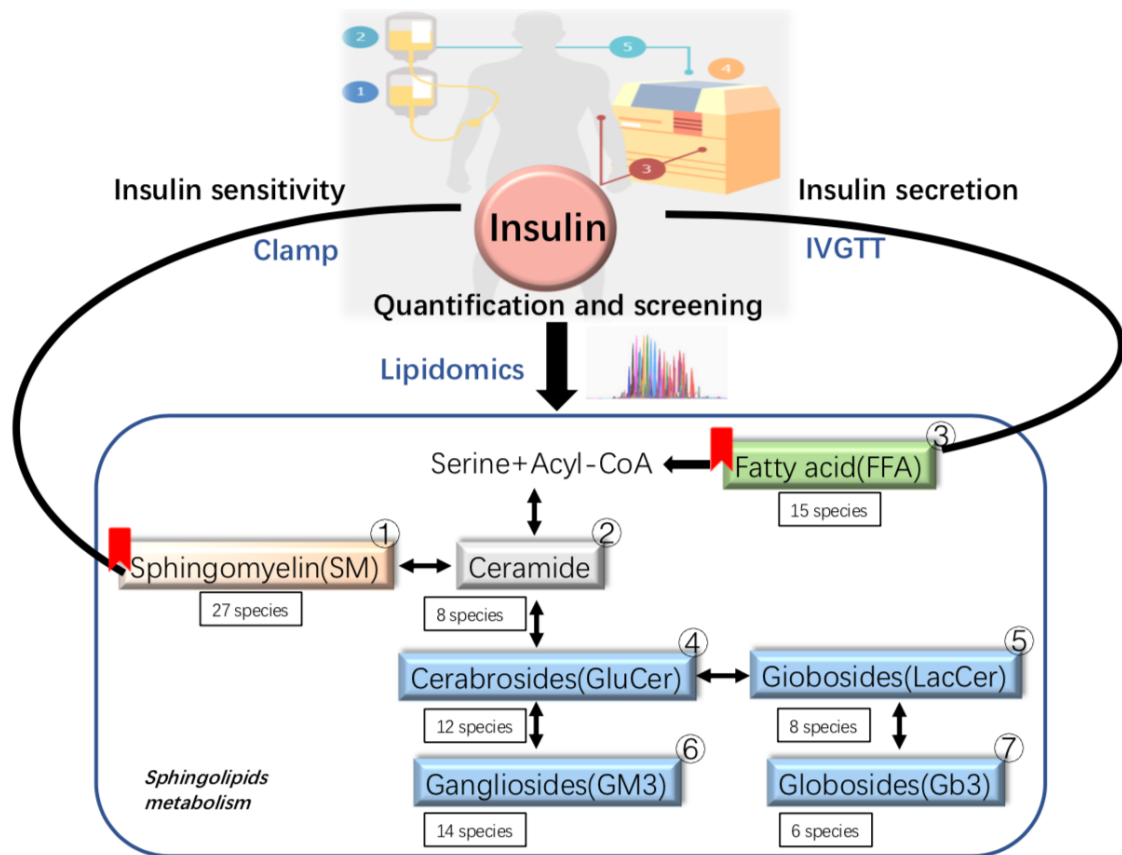
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558 perturbation of glycerophospholipids, fatty acids, and sphingolipids in diet-induced
559 hyperlipidemia. *Chem Biol Interact.* 2015;228:79-87.
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563 **Figure 1. Study design.**

564 Decreased insulin sensitivity is a multifactorial condition related to obesity, increased inflammation and
565 dyslipidemia. Lipotoxicity impairs islet function. Sphingolipids are a diverse class of lipids and we
566 aimed to systematically investigate the changes in serum lipids in individuals and uncover potential
567 serum sphingolipid predictors for insulin sensitivity and insulin secretion. Serum samples were
568 analyzed by a targeted lipidomics approach. The glucose infusion rate over 30 minutes (GIR₃₀) under
569 steady conditions was measured by the gold standard hyperinsulinemic-euglycemic clamp, and first-
570 phase insulin release (FPIR) was evaluated by the intravenous glucose tolerance test (IVGTT).

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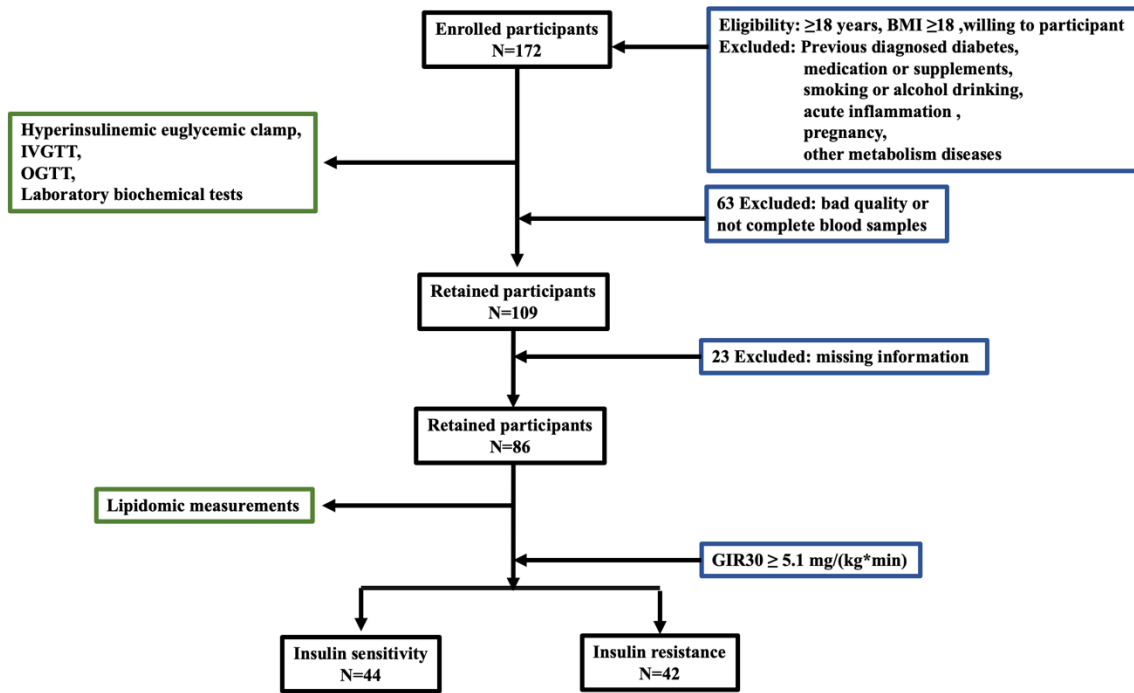
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578 **Figure 2. Flow chart of the study**

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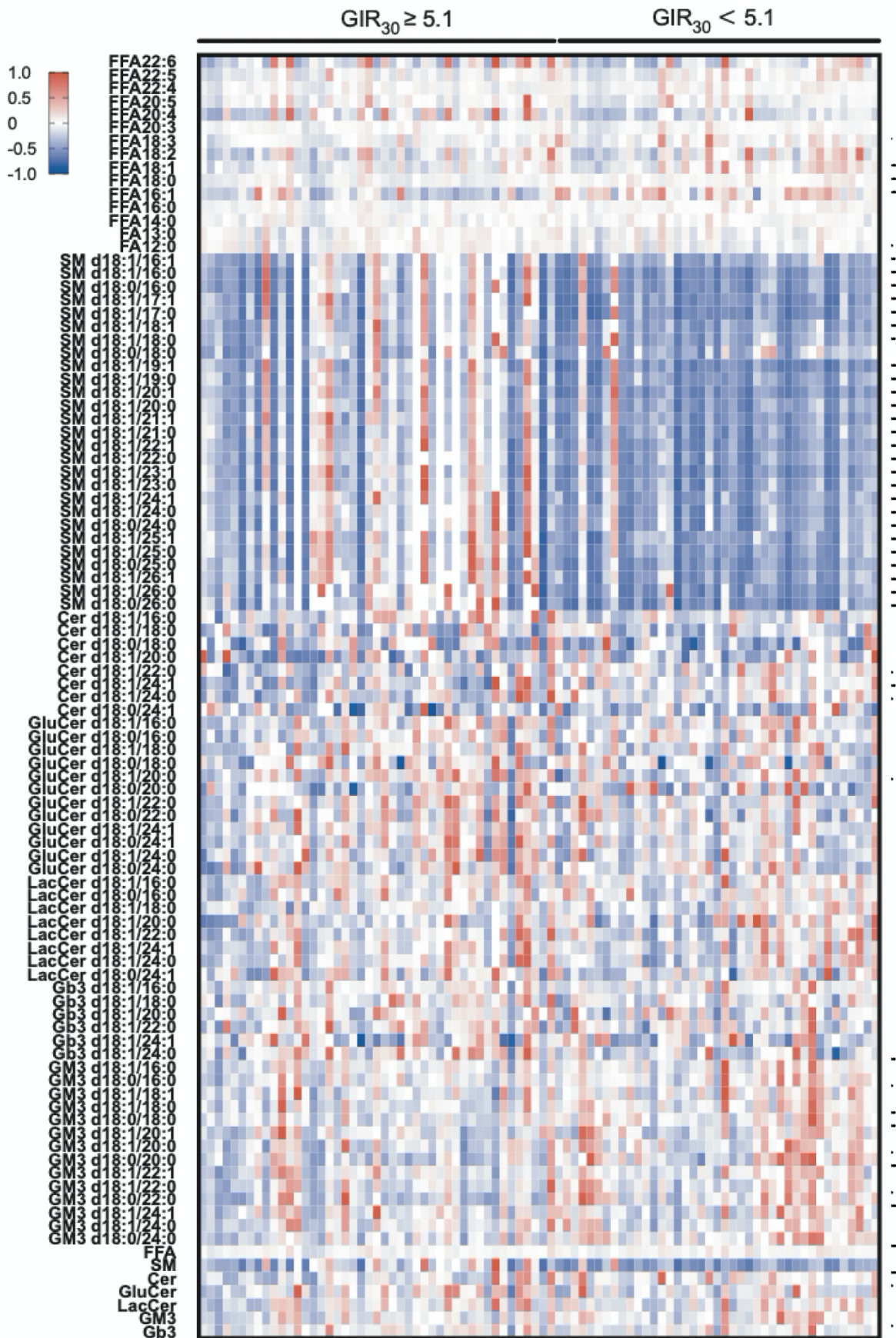
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Table 1 Participants' characteristics divided by GIR₃₀ (mg / (kg *min))

	Insulin sensitivity (GIR ₃₀ ≥ 5.1)		Insulin resistance (GIR ₃₀ < 5.1)		P value
	Mean ± SD	Median(range)	Mean ± SD	Median(range)	
No.(F)	44(25)		42(21)		0.53 ^a
Age (years)	27.6±8.1	25.0(18.0-53.0)	29.4±8.5	28(18.0-56.0)	0.08 ^b
BMI (kg/m ²)	26.2±7.5	23.3(18-47)	40.4±9.1	38.5(28.0-69.9)	<0.001 ^b
FBG (mmol/L)	5.1±0.6	4.9(4.2-7.1)	6.8±2.7	5.5(4.3-17.3)	<0.001 ^b
2hPG (mmol/L)	6.8±2.7	6.0(3.5-20)	11.1±4.6	10.7(3.7-21.6)	<0.001 ^c
TC (mmol/L)	4.4±0.8	4.2(2.8-6.3)	5.3±1.1	5.4(2.9-7.9)	<0.001 ^c
TG (mmol/L)	1.1±0.6	0.9(0.4-2.9)	2.6±3.7	1.8(0.7-23.9)	<0.001 ^b
HDL-c (mmol/L)	1.4±0.3	1.3(0.8-2.1)	1.1±0.2	1.1(0.7-1.6)	0.01 ^c
LDL-c (mmol/L)	2.6±0.7	2.5(1.0-4.5)	3.4±0.9	3.4(1.1-5.5)	<0.001 ^b
ALT (U/L)	32.7±33.0	18(8.0-160.6)	84.5±79.9	68.4(6.1-404.8)	<0.001 ^b
AST (U/L)	28.3±20.1	20.5(13.0-104.7)	58.0±56.1	43.2(11.2-319.0)	<0.001 ^b

594 F (female), body mass index (BMI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglyceride
595 (TG), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), fasting blood glucose (FBG), 2-hour
596 plasma glucose (2hPG). Data are presented as the mean ± SD or median (range). ^a x² test. ^b Mann-Whitney U test. ^c Independent samples t
597 test.



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600 **Figure 3. Serum lipid concentrations in individuals visualized by heatmap.**

601 Each colored cell on the map corresponds to a concentration value. The concentration values were
602 transformed to -1 (most below average, Blue) to 1 (most above average, Red). The 90 lipid species
603 from the two groups are presented and range from insulin sensitivity to IR. s: non-IR group, r IR
604 group.

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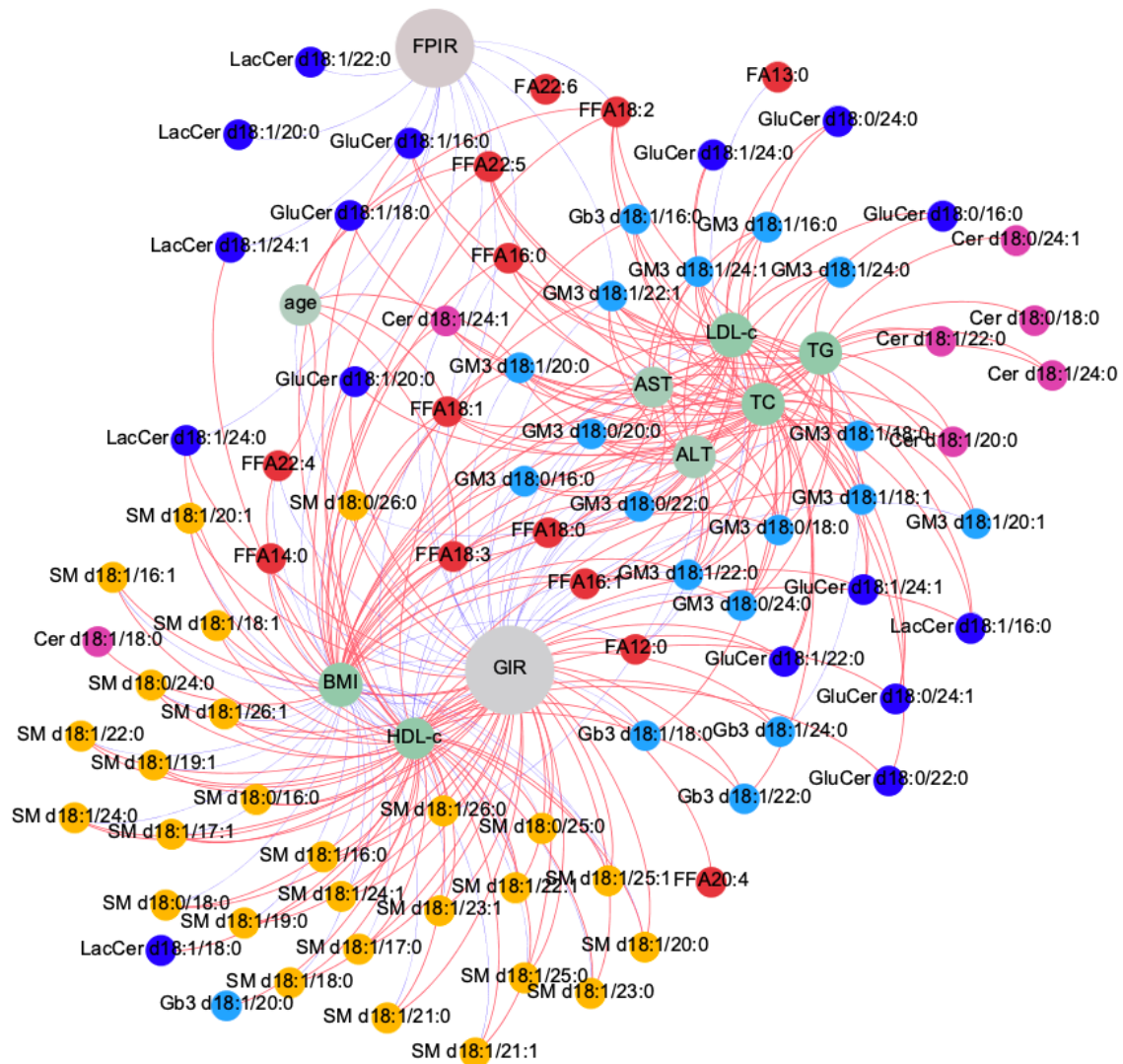
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625 **Figure 4. Correlations between serum lipids and multiple clinical characteristics.**

626 Clinical characteristics network showing lipid correlations with GIR, FPIR (grey nodes) and 8 key

627 clinical characteristics (green nodes). Pearson's correlation was analyzed (A) and absolute coefficient

628 values of 0.2 and above are shown ($P < 0.05$). Red edge color indicates positive correlation, while

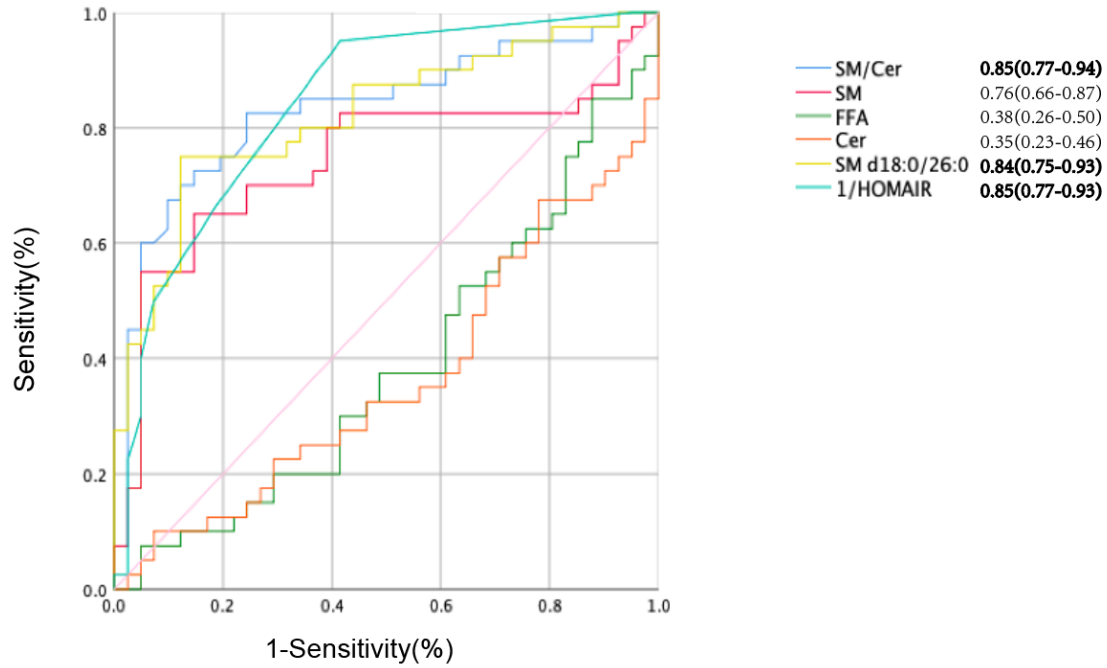
629 blue edge indicates negative correlation. Node color is grouped according to lipid type. SM nodes are

630 yellow, ceramide nodes are pink, GluCer and LacCer nodes are dark blue, FFA nodes are red, and

631 GM3 and Gb3 nodes are blue.

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637 **Figure 5. Different noninvasive clinical models or serum biomarkers for defining IR.**

638 Plots of area under the curves (AUC) in the total subjects using $GIR \geq 5.1$ mg / (kg *min) as a reference.

639 SM, total serum sphingomyelins; FFA, total serum fatty acids; Cer, total serum ceramides; SM/Cer,

640 total serum sphingomyelins/ total serum ceramides. Model 1: 1/HOMAIR, AUC 0.852; Model 2:

641 SM/Ceramide, AUC 0.851; Model 3, SM d18:0/26:0, AUC 0.839.

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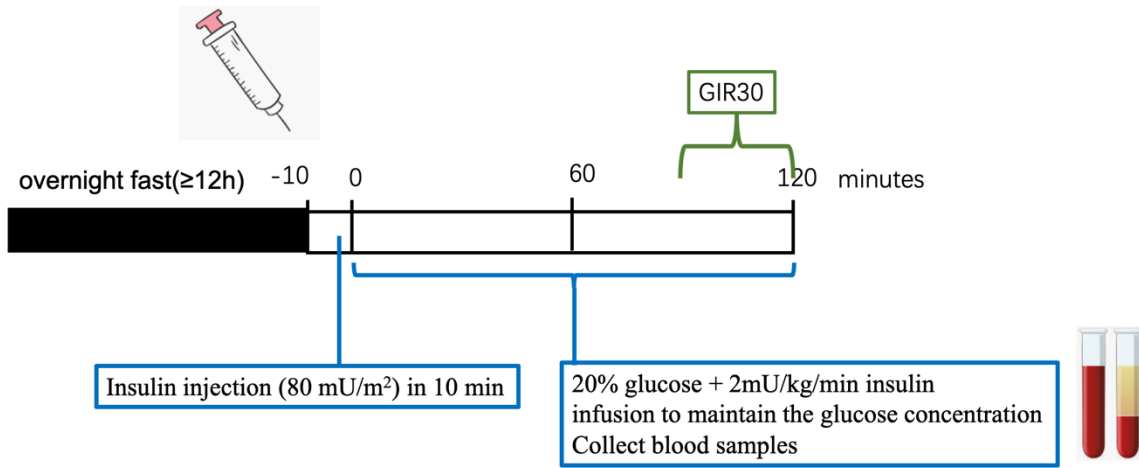
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Supplemental Material

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681 **Supplementary Figure 1. Flow chart of the hyperinsulinemic euglycemic clamp.**

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701 **Supplementary Table 1** Gender differences in individual lipid species

Lipid	Male (n=40)		Female(n=46)		P value		
	Average lipid concentration (nM)	Standard deviation	Average lipid concentration (nM)	Standard deviation	t.test	Man whitney u test	Percentage changed in Female /Male
FFA22:6	27,383.80	9,766.63	28,364.37	11,811.23	0.679	0.91	4%
FFA22:5	35,394.50	5,727.76	34,595.93	5,745.34	0.521	0.391	-2%
FFA22:4	46,630.81	5,410.97	45,155.79	4,303.44	0.163	0.307	-3%
FFA20:5	38,193.91	7,044.16	37,642.25	6,542.37	0.708	0.516	-1%
FFA20:4	70,539.58	25,512.53	72,809.47	34,369.68	0.732	0.511	3%
FFA20:3	72,926.12	7,350.62	71,428.02	5,230.23	0.275	0.489	-2%
FFA18:3	21,382.20	4,770.98	20,105.87	2,522.77	0.135	0.345	-6%
FFA18:2	833,119.63	289,535.66	757,961.14	216,305.49	0.173	0.287	-9%
FFA18:1	368,217.17	80,349.19	353,921.66	64,141.91	0.362	0.494	-4%
FFA18:0	2,444,736.12	204,479.00	2,492,478.17	245,099.65	0.334	0.319	2%
FFA16:1	898,803.53	283,053.74	868,390.86	265,350.32	0.609	0.71	-3%
FFA16:0	2,643,907.12	201,659.98	2,667,694.84	222,784.21	0.607	0.505	1%
FFA14:0	231,903.36	21,691.50	228,117.15	19,882.60	0.401	0.446	-2%
FA13:0	1,393,717.86	189,564.71	1,381,101.56	165,049.25	0.742	0.368	-1%
FA12:0	1,573,313.86	215,239.69	1,563,687.31	209,107.91	0.834	0.337	-1%
SM d18:1/16:1	30,057.81	24,607.53	47,297.16	68,494.93	0.117	0.239	57%
SM d18:1/16:0	261,682.84	304,651.82	424,500.72	774,554.29	0.194	0.382	62%
SM d18:0/16:0	26,831.28	30,257.85	44,211.40	81,235.64	0.183	0.319	65%
SM d18:1/17:1	726.56	905.01	1,177.57	1,974.57	0.169	0.242	62%
SM d18:1/17:0	5,109.41	6,623.18	7,895.05	14,079.59	0.255	0.499	55%
SM d18:1/18:1	23,088.56	24,590.08	38,873.03	62,262.07	0.119	0.069	68%
SM d18:1/18:0	50,774.22	50,941.15	79,784.17	127,935.06	0.162	0.188	57%
SM d18:0/18:0	7,032.74	6,030.26	10,154.18	13,865.24	0.191	0.194	44%
SM d18:1/19:1	684.52	845.61	1,210.39	2,119.81	0.127	0.139	77%
SM d18:1/19:0	2,545.16	3,091.95	3,878.42	6,239.70	0.224	0.275	52%
SM d18:1/20:1	12,017.58	13,461.09	20,731.21	35,472.11	0.128	0.242	73%
SM d18:1/20:0	34,826.78	38,237.52	52,655.08	90,131.98	0.248	0.562	51%
SM d18:1/21:1	1,429.28	1,537.62	2,423.55	3,745.42	0.104	0.052	70%
SM d18:1/21:0	7,361.64	8,314.51	10,675.81	18,391.14	0.297	0.653	45%
SM d18:1/22:1	46,827.61	49,136.37	73,389.35	127,557.32	0.219	0.494	57%
SM d18:1/22:0	74,840.63	73,026.20	106,707.91	179,906.53	0.298	0.856	43%
SM d18:1/23:1	18,081.48	21,213.37	28,329.23	47,768.35	0.214	0.287	57%
SM d18:1/23:0	26,908.03	29,048.26	38,383.33	60,875.30	0.279	0.527	43%
SM d18:1/24:1	157,301.00	171,533.25	212,925.04	327,984.16	0.338	0.609	35%
SM d18:1/24:0	65,451.44	61,345.47	86,713.95	141,494.70	0.381	0.802	32%
SM d18:0/24:0	6,869.94	5,980.68	8,853.64	14,267.69	0.415	0.634	29%
SM d18:1/25:1	3,632.10	4,145.74	4,844.12	6,596.36	0.319	0.467	33%
SM d18:1/25:0	2,952.53	3,086.90	4,099.75	6,241.02	0.294	0.762	39%
SM d18:0/25:0	1,719.97	1,898.90	2,537.14	4,147.75	0.255	0.579	48%
SM d18:1/26:1	1,076.02	1,129.34	1,386.10	1,942.26	0.377	0.808	29%
SM d18:1/26:0	548.73	486.92	702.80	921.36	0.346	0.835	28%
SM d18:0/26:0	236.94	219.39	316.85	422.50	0.266	0.849	34%
Cer d18:1/16:0	733.94	326.00	723.88	286.79	0.879	0.924	-1%
Cer d18:1/18:0	424.96	373.33	362.53	216.39	0.338	0.467	-15%
Cer d18:0/18:0	252.42	239.77	250.46	198.62	0.967	0.457	-1%
Cer d18:1/20:0	359.80	392.06	278.40	247.02	0.246	0.1	-23%
Cer d18:1/22:0	997.55	430.14	1,056.45	515.93	0.57	0.703	6%
Cer d18:1/24:1	2,181.16	1,118.76	2,248.25	1,577.70	0.823	0.835	3%
Cer d18:1/24:0	3,080.36	1,228.06	3,046.26	1,635.38	0.914	0.489	-1%
Cer d18:0/24:1	209.60	178.50	214.47	171.01	0.898	0.924	2%

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GluCer d18:1/16:0	750.59	316.45	761.92	237.13	0.85	0.603	2%
GluCer d18:0/16:0	27.41	9.86	26.78	8.36	0.747	0.788	-2%
GluCer d18:1/18:0	94.80	36.00	110.10	41.65	0.074	0.089	16%
GluCer d18:0/18:0	6.98	4.18	8.03	2.97	0.181	0.039	15%
GluCer d18:1/20:0	84.58	33.41	92.00	29.93	0.281	0.315	9%
GluCer d18:0/20:0	6.69	3.12	6.28	3.67	0.586	0.268	-6%
GluCer d18:1/22:0	732.92	310.43	725.66	274.95	0.909	0.931	-1%
GluCer d18:0/22:0	17.73	7.74	18.76	7.80	0.541	0.71	6%
GluCer d18:1/24:1	930.28	317.27	984.06	283.66	0.409	0.446	6%
GluCer d18:0/24:1	963.37	420.63	914.51	371.85	0.569	0.516	-5%
GluCer d18:1/24:0	26.80	12.40	27.27	9.93	0.846	0.562	2%
GluCer d18:0/24:0	22.61	10.17	21.22	8.83	0.502	0.373	-6%
LacCer d18:1/16:0	3,319.71	1,121.12	3,200.51	834.62	0.582	0.965	-4%
LacCer d18:0/16:0	78.57	24.46	76.37	21.47	0.658	0.749	-3%
LacCer d18:1/18:0	100.88	33.04	101.01	63.47	0.991	0.377	0%
LacCer d18:1/20:0	40.34	17.09	42.25	24.07	0.677	0.924	5%
LacCer d18:1/22:0	181.20	73.18	176.46	97.89	0.802	0.436	-3%
LacCer d18:1/24:1	660.40	251.70	638.00	222.82	0.663	0.775	-3%
LacCer d18:1/24:0	266.52	105.28	267.49	136.44	0.971	0.938	0%
LacCer d18:0/24:1	18.75	8.79	16.06	6.37	0.104	0.203	-14%
Gb3 d18:1/16:0	1,412.52	378.84	1,452.58	326.65	0.6	0.483	3%
Gb3 d18:1/18:0	160.89	51.28	167.72	56.60	0.561	0.755	4%
Gb3 d18:1/20:0	63.95	26.70	74.61	23.52	0.052	0.009	17%
Gb3 d18:1/22:0	206.38	70.35	224.67	78.68	0.262	0.332	9%
Gb3 d18:1/24:1	27.45	15.06	25.83	14.33	0.611	0.671	-6%
Gb3 d18:1/24:0	81.59	28.43	77.97	31.65	0.58	0.467	-4%
GM3 d18:1/16:0	3,403.98	967.45	3,295.38	790.38	0.568	0.788	-3%
GM3 d18:0/16:0	723.50	220.45	686.62	163.95	0.377	0.849	-5%
GM3 d18:1/18:1	387.44	119.25	359.98	123.08	0.298	0.246	-7%
GM3 d18:1/18:0	1,559.14	427.58	1,301.05	362.73	0.003	0.003	-17%
GM3 d18:0/18:0	562.20	125.24	508.78	141.29	0.069	0.038	-10%
GM3 d18:1/20:1	194.20	67.06	188.98	67.63	0.721	0.723	-3%
GM3 d18:1/20:0	698.33	251.91	594.50	191.91	0.037	0.045	-15%
GM3 d18:0/20:0	191.02	71.34	168.85	69.51	0.149	0.109	-12%
GM3 d18:1/22:1	873.83	285.60	828.96	233.36	0.425	0.808	-5%
GM3 d18:1/22:0	1,949.95	689.83	1,735.82	565.09	0.117	0.13	-11%
GM3 d18:0/22:0	531.34	214.52	465.81	211.41	0.158	0.096	-12%
GM3 d18:1/24:1	2,522.35	821.36	2,343.51	729.56	0.288	0.337	-7%
GM3 d18:1/24:0	1,938.94	625.09	1,683.28	456.44	0.036	0.06	-13%
GM3 d18:0/24:0	477.69	137.55	466.07	138.48	0.698	0.622	-2%
FFA	10,700,169.57	895,473.03	10,623,454.39	947,850.78	0.702	0.634	-1%
SM	870,614.80	928,565.89	1,314,656.93	2,215,685.17	0.241	0.544	51%
Cer	8,239.79	2,722.51	8,180.70	3,918.70	0.936	0.426	-1%
GluCer	3,664.76	1,394.08	3,696.58	1,189.34	0.909	0.869	1%
LacCer	4,666.37	1,536.55	4,518.14	1,260.03	0.624	0.89	-3%
GM3	16,013.92	4,316.51	14,627.60	3,612.06	0.109	0.136	-9%
Gb3	1,952.78	499.64	2,023.37	471.45	0.502	0.653	4%
SM/Cer	108.53	114.39	180.94	301.07	0.136	0.539	67%

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708 **Supplementary Table 2** Age differences in individual lipid species

Lipids	Age ≤ 26 (n=43)		Age > 26 (n=43)		P value		Percentage changed in age
	Average lipid concentration (nM)	Standard deviation	Average lipid concentration (nM)	Standard deviation	t.test	Man whitney u test	
FFA22:6	25,664.85	10,909.68	30,151.73	10,450.19	0.055	0.009	17%
FFA22:5	32,676.18	4,628.27	37,258.53	5,829.72	0.000	0.000	14%
FFA22:4	44,495.41	3,982.61	47,188.29	5,344.60	0.010	0.023	6%
FFA20:5	37,143.60	7,624.72	38,654.07	5,725.95	0.302	0.049	4%
FFA20:4	69,792.26	29,525.78	73,715.15	31,512.28	0.553	0.113	6%
FFA20:3	70,432.19	5,427.57	73,817.44	6,730.52	0.012	0.008	5%
FFA18:3	19,424.87	2,551.20	21,974.15	4,353.13	0.001	0.001	13%
FFA18:2	694,918.69	193,721.87	890,918.47	271,398.54	0.000	0.000	28%
FFA18:1	330,532.70	53,962.63	390,608.76	75,812.34	0.000	0.000	18%
FFA18:0	2,406,859.07	237,006.03	2,533,686.06	199,862.86	0.009	0.010	5%
FFA16:1	838,192.23	270,514.95	926,880.34	270,375.93	0.132	0.111	11%
FFA16:0	2,596,906.98	213,413.67	2,716,354.58	195,905.92	0.008	0.004	5%
FFA14:0	225,165.36	20,514.97	234,591.00	20,035.65	0.034	0.073	4%
FA13:0	1,383,897.97	184,211.09	1,390,041.25	169,360.87	0.872	0.65	0%
FA12:0	1,574,468.00	218,118.19	1,561,861.55	205,569.19	0.783	0.969	-1%
SM d18:1/16:1	47,803.64	70,685.87	30,754.08	24,393.51	0.139	0.323	-36%
SM d18:1/16:0	448,597.44	798,519.85	248,945.51	290,577.87	0.127	0.2	-45%
SM d18:0/16:0	46,260.37	83,806.11	25,994.88	28,998.68	0.138	0.222	-44%
SM d18:1/17:1	1,207.23	2,033.47	728.37	888.38	0.161	0.263	-40%
SM d18:1/17:0	8,352.34	14,503.31	4,846.46	6,359.45	0.150	0.171	-42%
SM d18:1/18:1	39,237.53	64,227.32	23,825.31	24,395.07	0.145	0.185	-39%
SM d18:1/18:0	81,892.35	131,904.76	50,689.99	49,775.32	0.150	0.245	-38%
SM d18:0/18:0	10,140.52	14,339.18	7,264.17	5,904.19	0.227	0.694	-28%
SM d18:1/19:1	1,255.75	2,181.41	675.86	829.90	0.107	0.061	-46%
SM d18:1/19:0	3,973.47	6,438.94	2,543.12	2,998.39	0.190	0.336	-36%
SM d18:1/20:1	21,452.24	36,504.16	11,904.48	13,261.38	0.111	0.121	-45%
SM d18:1/20:0	54,530.10	92,935.16	34,195.59	37,081.26	0.186	0.385	-37%
SM d18:1/21:1	2,442.31	3,865.52	1,479.89	1,520.77	0.132	0.188	-39%
SM d18:1/21:0	11,098.66	18,995.34	7,170.01	7,966.07	0.215	0.487	-35%
SM d18:1/22:1	77,117.32	131,391.34	44,952.78	47,340.52	0.135	0.132	-42%
SM d18:1/22:0	113,955.80	185,271.33	69,816.03	69,459.72	0.147	0.168	-39%
SM d18:1/23:1	29,840.28	49,233.44	17,285.38	20,286.50	0.126	0.141	-42%
SM d18:1/23:0	40,411.11	62,807.51	25,680.85	27,663.27	0.163	0.218	-36%
SM d18:1/24:1	225,164.02	337,144.44	148,942.76	165,876.97	0.187	0.121	-34%
SM d18:1/24:0	93,791.48	145,581.58	59,857.34	58,241.73	0.160	0.197	-36%
SM d18:0/24:0	9,596.96	14,682.48	6,265.02	5,662.81	0.169	0.302	-35%
SM d18:1/25:1	5,074.90	6,751.28	3,485.87	4,056.53	0.189	0.046	-31%
SM d18:1/25:0	4,351.82	6,397.48	2,780.50	3,009.93	0.149	0.086	-36%
SM d18:0/25:0	2,703.21	4,256.07	1,610.91	1,842.91	0.126	0.065	-40%
SM d18:1/26:1	1,476.26	1,987.36	1,007.49	1,101.38	0.180	0.07	-32%
SM d18:1/26:0	774.38	949.39	487.90	445.45	0.077	0.123	-37%
SM d18:0/26:0	347.91	429.81	211.46	211.98	0.065	0.07	-39%
Cer d18:1/16:0	733.36	278.67	723.76	330.39	0.885	0.434	-1%
Cer d18:1/18:0	396.83	217.33	386.31	366.45	0.872	0.228	-3%
Cer d18:0/18:0	250.92	195.82	251.82	239.39	0.985	0.543	0%
Cer d18:1/20:0	288.39	180.52	344.14	421.08	0.427	0.839	19%
Cer d18:1/22:0	994.94	515.38	1,063.16	436.77	0.510	0.235	7%
Cer d18:1/24:1	1,884.11	859.78	2,549.98	1,692.71	0.024	0.038	35%
Cer d18:1/24:0	2,705.28	1,173.58	3,418.96	1,621.26	0.022	0.012	26%
Cer d18:0/24:1	199.25	128.68	225.16	209.82	0.492	0.4	13%

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GluCer d18:1/16:0	780.49	293.25	732.81	257.19	0.425	0.694	-6%
GluCer d18:0/16:0	27.49	9.59	26.66	8.55	0.674	0.806	-3%
GluCer d18:1/18:0	102.43	40.86	103.53	38.87	0.898	0.575	1%
GluCer d18:0/18:0	8.07	3.61	7.01	3.55	0.172	0.245	-13%
GluCer d18:1/20:0	88.98	34.66	88.12	28.69	0.900	0.894	-1%
GluCer d18:0/20:0	6.53	3.36	6.41	3.50	0.874	0.792	-2%
GluCer d18:1/22:0	747.40	327.65	710.68	249.93	0.561	0.931	-5%
GluCer d18:0/22:0	19.35	8.13	17.21	7.27	0.202	0.308	-11%
GluCer d18:1/24:1	982.35	324.90	935.74	272.91	0.473	0.839	-5%
GluCer d18:0/24:1	961.44	444.42	913.03	339.03	0.572	0.99	-5%
GluCer d18:1/24:0	27.18	11.99	26.92	10.22	0.912	0.863	-1%
GluCer d18:0/24:0	23.29	10.37	20.44	8.30	0.162	0.284	-12%
LacCer d18:1/16:0	3,116.73	927.56	3,395.17	1,010.28	0.187	0.158	9%
LacCer d18:0/16:0	75.82	24.32	78.97	21.33	0.524	0.429	4%
LacCer d18:1/18:0	104.41	64.03	97.49	34.72	0.535	0.736	-7%
LacCer d18:1/20:0	42.88	25.26	39.85	15.85	0.508	0.789	-7%
LacCer d18:1/22:0	178.95	103.59	178.38	67.23	0.976	0.492	0%
LacCer d18:1/24:1	660.78	255.14	636.05	216.49	0.629	0.894	-4%
LacCer d18:1/24:0	271.48	146.86	262.59	92.89	0.738	0.812	-3%
LacCer d18:0/24:1	17.04	6.83	17.58	8.49	0.744	0.832	3%
Gb3 d18:1/16:0	1,398.17	314.51	1,469.74	383.23	0.347	0.218	5%
Gb3 d18:1/18:0	160.73	53.32	168.35	55.00	0.516	0.442	5%
Gb3 d18:1/20:0	71.47	24.72	67.83	26.36	0.510	0.344	-5%
Gb3 d18:1/22:0	213.78	69.17	218.54	81.25	0.771	0.969	2%
Gb3 d18:1/24:1	26.62	10.46	26.54	17.96	0.980	0.252	0%
Gb3 d18:1/24:0	80.69	29.30	78.62	31.14	0.752	0.887	-3%
GM3 d18:1/16:0	3,164.27	745.19	3,527.52	959.98	0.053	0.059	11%
GM3 d18:0/16:0	656.82	172.45	750.74	200.90	0.022	0.027	14%
GM3 d18:1/18:1	352.47	114.04	393.04	126.39	0.122	0.121	12%
GM3 d18:1/18:0	1,331.05	361.03	1,511.14	444.67	0.042	0.088	14%
GM3 d18:0/18:0	518.18	123.86	549.07	146.89	0.295	0.455	6%
GM3 d18:1/20:1	182.87	73.94	199.95	58.94	0.240	0.047	9%
GM3 d18:1/20:0	582.33	206.64	703.26	231.72	0.012	0.009	21%
GM3 d18:0/20:0	168.35	69.42	189.97	71.38	0.158	0.102	13%
GM3 d18:1/22:1	785.34	231.35	914.33	270.32	0.020	0.026	16%
GM3 d18:1/22:0	1,669.14	552.09	2,001.69	667.80	0.014	0.011	20%
GM3 d18:0/22:0	430.96	182.68	561.61	225.16	0.004	0.001	30%
GM3 d18:1/24:1	2,292.58	758.54	2,560.80	775.11	0.109	0.098	12%
GM3 d18:1/24:0	1,697.03	521.51	1,907.36	569.85	0.078	0.059	12%
GM3 d18:0/24:0	435.18	133.48	507.77	132.93	0.013	0.010	17%
FFA	10,350,570.37	866,866.65	10,967,701.37	873,939.57	0.001	0.003	6%
SM	1,382,849.40	2,282,469.10	833,402.02	892,639.92	0.145	0.191	-40%
Cer	7,453.08	2,426.09	8,963.28	4,035.35	0.038	0.035	20%
GluCer	3,775.01	1,434.61	3,588.55	1,115.71	0.503	0.983	-5%
LacCer	4,468.08	1,426.28	4,706.09	1,356.97	0.430	0.271	5%
GM3	14,266.55	3,661.59	16,278.25	4,096.39	0.019	0.019	14%
Gb3	1,951.46	441.57	2,029.62	523.81	0.456	0.323	4%
SM/Cer	192.98	307.62	101.54	114.15	0.071	0.005	-47%

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715 **Supplementary Table 3** BMI differences in individual lipid species

Lipid	BMI ≤ 30(n=34)		BMI > 30(n=52)		P value		Percentage changed in BMI
	Average lipid concentration (nM)	Standard deviation	Average lipid concentration (nM)	Standard deviation	t.test	Man whitney u test	
FFA22:6	28,078.23	12,368.87	27,797.17	9,869.88	0.907	0.566	-1%
FFA22:5	33,321.12	5,503.46	36,043.74	5,647.54	0.030	0.016	8%
FFA22:4	44,312.67	4,178.58	46,841.70	5,076.11	0.018	0.033	6%
FFA20:5	38,560.37	7,642.17	37,466.30	6,129.19	0.465	0.314	-3%
FFA20:4	78,129.91	34,027.62	67,584.65	27,352.51	0.117	0.179	-13%
FFA20:3	71,944.61	4,630.44	72,242.64	7,244.83	0.832	0.888	0%
FFA18:3	19,197.70	1,903.41	21,681.46	4,344.47	0.002	0.005	13%
FFA18:2	716,912.44	202,382.81	842,614.90	273,655.14	0.024	0.026	18%
FFA18:1	326,522.06	50,065.75	382,833.32	75,846.63	0.000	0.000	17%
FFA18:0	2,341,076.75	228,413.05	2,554,746.75	183,776.91	0.000	0.000	9%
FFA16:1	704,815.69	170,654.92	998,738.22	264,791.55	0.000	0.000	42%
FFA16:0	2,589,493.93	200,408.96	2,700,527.95	210,169.41	0.017	0.007	4%
FFA14:0	225,100.94	21,412.92	233,001.76	19,818.84	0.084	0.145	4%
FA13:0	1,449,118.91	131,812.46	1,346,333.52	189,951.78	0.007	0.010	-7%
FA12:0	1,674,743.20	152,780.30	1,498,478.89	215,454.45	0.000	0.000	-11%
SM d18:1/16:1	60,565.24	79,183.95	25,360.84	13,062.66	0.002	0.000	-58%
SM d18:1/16:0	611,441.82	902,116.67	177,025.48	93,762.93	0.001	0.000	-71%
SM d18:0/16:0	61,724.06	94,785.90	19,391.49	10,672.34	0.002	0.000	-69%
SM d18:1/17:1	1,680.50	2,326.77	501.80	297.96	0.001	0.000	-70%
SM d18:1/17:0	11,710.72	16,663.35	3,257.39	1,800.38	0.000	0.000	-72%
SM d18:1/18:1	50,935.49	73,338.30	18,844.14	9,595.42	0.002	0.000	-63%
SM d18:1/18:0	104,925.51	150,936.34	41,030.26	19,809.65	0.003	0.000	-61%
SM d18:0/18:0	11,731.39	16,438.16	6,721.82	4,069.80	0.038	0.179	-43%
SM d18:1/19:1	1,728.26	2,464.62	467.27	237.34	0.000	0.000	-73%
SM d18:1/19:0	5,470.81	7,495.70	1,811.65	810.68	0.001	0.000	-67%
SM d18:1/20:1	29,081.30	41,074.13	8,568.75	4,404.92	0.001	0.000	-71%
SM d18:1/20:0	73,886.08	106,489.76	25,059.19	10,988.69	0.001	0.000	-66%
SM d18:1/21:1	3,295.58	4,375.20	1,088.55	500.72	0.001	0.000	-67%
SM d18:1/21:0	15,484.78	21,775.64	4,982.12	2,151.46	0.001	0.000	-68%
SM d18:1/22:1	105,030.06	147,834.73	32,269.08	14,943.29	0.001	0.000	-69%
SM d18:1/22:0	153,109.78	209,369.69	51,854.93	23,781.50	0.001	0.000	-66%
SM d18:1/23:1	41,679.97	55,757.39	11,717.01	5,293.20	0.000	0.000	-72%
SM d18:1/23:0	55,801.62	71,746.16	18,167.29	8,285.92	0.000	0.000	-67%
SM d18:1/24:1	302,621.24	396,328.89	111,489.80	48,505.44	0.001	0.000	-63%
SM d18:1/24:0	126,778.10	164,810.13	44,162.38	20,145.88	0.001	0.000	-65%
SM d18:0/24:0	12,857.67	16,537.36	4,709.70	2,213.39	0.001	0.000	-63%
SM d18:1/25:1	6,946.61	8,161.53	2,537.09	1,101.59	0.000	0.000	-63%
SM d18:1/25:0	5,995.87	7,358.96	1,977.50	810.54	0.000	0.000	-67%
SM d18:0/25:0	3,771.08	4,836.57	1,101.74	457.07	0.000	0.000	-71%
SM d18:1/26:1	2,022.01	2,343.12	731.78	347.42	0.000	0.000	-64%
SM d18:1/26:0	1,056.00	1,032.92	353.35	225.65	0.000	0.000	-67%
SM d18:0/26:0	490.32	466.67	141.96	84.59	0.000	0.000	-71%
Cer d18:1/16:0	768.32	260.13	702.55	329.17	0.329	0.050	-9%
Cer d18:1/18:0	406.48	238.88	381.82	335.20	0.711	0.354	-6%
Cer d18:0/18:0	295.69	204.71	222.40	222.47	0.127	0.010	-25%
Cer d18:1/20:0	303.88	178.48	324.36	391.64	0.776	0.442	7%
Cer d18:1/22:0	959.13	515.51	1,074.77	447.73	0.273	0.082	12%
Cer d18:1/24:1	1,818.55	945.36	2,477.60	1,549.82	0.029	0.006	36%
Cer d18:1/24:0	2,853.35	1,242.83	3,198.62	1,570.38	0.261	0.247	12%
Cer d18:0/24:1	219.19	177.70	207.64	172.31	0.765	0.784	-5%

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GluCer d18:1/16:0	784.60	245.30	738.37	294.03	0.450	0.372	-6%
GluCer d18:0/16:0	27.48	7.82	26.80	9.82	0.735	0.612	-2%
GluCer d18:1/18:0	109.77	45.36	98.55	35.18	0.201	0.440	-10%
GluCer d18:0/18:0	7.81	3.24	7.36	3.84	0.574	0.668	-6%
GluCer d18:1/20:0	98.59	31.76	81.98	30.06	0.016	0.023	-17%
GluCer d18:0/20:0	6.63	3.27	6.37	3.53	0.728	0.422	-4%
GluCer d18:1/22:0	818.39	301.50	670.62	269.81	0.020	0.020	-18%
GluCer d18:0/22:0	19.89	8.06	17.23	7.42	0.120	0.185	-13%
GluCer d18:1/24:1	998.62	287.32	933.17	306.66	0.324	0.354	-7%
GluCer d18:0/24:1	1,021.02	377.25	882.46	398.10	0.108	0.040	-14%
GluCer d18:1/24:0	28.43	11.08	26.15	11.09	0.355	0.223	-8%
GluCer d18:0/24:0	22.64	9.62	21.36	9.39	0.547	0.480	-6%
LacCer d18:1/16:0	3,244.60	931.64	3,263.37	1,009.96	0.931	0.993	1%
LacCer d18:0/16:0	75.33	23.28	78.75	22.60	0.500	0.522	5%
LacCer d18:1/18:0	109.00	71.30	95.69	32.07	0.242	0.260	-12%
LacCer d18:1/20:0	39.60	25.97	42.52	17.22	0.532	0.162	7%
LacCer d18:1/22:0	188.97	107.44	171.93	70.53	0.377	0.590	-9%
LacCer d18:1/24:1	686.51	239.04	623.51	232.14	0.231	0.210	-9%
LacCer d18:1/24:0	293.83	150.47	249.52	97.27	0.101	0.122	-15%
LacCer d18:0/24:1	18.94	6.29	16.25	8.33	0.112	0.023	-14%
Gb3 d18:1/16:0	1,475.01	341.95	1,407.10	356.44	0.383	0.349	-5%
Gb3 d18:1/18:0	178.08	54.45	155.69	52.31	0.060	0.053	-13%
Gb3 d18:1/20:0	74.52	23.04	66.47	26.67	0.153	0.077	-11%
Gb3 d18:1/22:0	233.66	73.99	204.72	74.21	0.080	0.087	-12%
Gb3 d18:1/24:1	27.39	10.71	26.06	16.76	0.682	0.207	-5%
Gb3 d18:1/24:0	89.96	27.76	72.92	29.86	0.009	0.007	-19%
GM3 d18:1/16:0	3,230.66	743.80	3,421.24	948.30	0.325	0.458	6%
GM3 d18:0/16:0	656.38	157.53	734.77	207.16	0.064	0.097	12%
GM3 d18:1/18:1	358.22	118.33	382.26	123.55	0.372	0.432	7%
GM3 d18:1/18:0	1,298.21	345.54	1,501.44	435.82	0.025	0.023	16%
GM3 d18:0/18:0	483.70	102.38	566.27	145.86	0.005	0.006	17%
GM3 d18:1/20:1	178.66	66.49	199.74	66.68	0.155	0.099	12%
GM3 d18:1/20:0	579.67	201.64	684.08	234.19	0.036	0.042	18%
GM3 d18:0/20:0	150.55	51.11	197.87	75.95	0.002	0.003	31%
GM3 d18:1/22:1	782.38	256.58	893.93	252.30	0.050	0.034	14%
GM3 d18:1/22:0	1,697.25	591.60	1,925.75	646.05	0.101	0.067	13%
GM3 d18:0/22:0	412.66	174.55	550.96	221.37	0.003	0.001	34%
GM3 d18:1/24:1	2,341.85	777.60	2,482.17	774.44	0.414	0.406	6%
GM3 d18:1/24:0	1,813.16	540.12	1,795.02	566.71	0.883	0.832	-1%
GM3 d18:0/24:0	422.36	111.48	503.59	144.03	0.007	0.012	19%
FFA	10,341,328.54	848,045.43	10,866,932.97	911,963.04	0.009	0.008	5%
SM	1,861,821.87	2,598,307.35	615,324.37	281,122.01	0.001	0.000	-67%
Cer	7,624.58	2,632.94	8,589.76	3,789.19	0.199	0.138	13%
GluCer	3,943.86	1,257.22	3,510.42	1,279.15	0.126	0.092	-11%
LacCer	4,656.76	1,420.62	4,541.53	1,379.99	0.711	0.757	-2%
GM3	14,405.69	3,703.54	15,839.10	4,106.46	0.104	0.100	10%
Gb3	2,078.62	483.12	1,932.95	479.09	0.173	0.112	-7%
SM/Cer	257.28	346.65	75.33	32.93	0.000	0.000	-71%

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720 **Supplementary Table 4** GIR differences in individual lipid species

Lipid	GIR < 5.1 (n=42)		GIR ≥ 5.1 (n=44)		P value		Percentage changed in GIR
	Average lipid concentration (nM)	Standard deviation	Average lipid concentration (nM)	Standard deviation	t.test	Man whitney u test	
FFA22:6	26,607.05	9,332.87	29,150.38	12,112.08	0.280	0.622	10%
FFA22:5	35,920.88	5,979.61	34,057.17	5,365.49	0.132	0.154	-5%
FFA22:4	46,854.61	5,184.60	44,875.12	4,408.02	0.059	0.104	-4%
FFA20:5	37,059.56	5,921.87	38,699.97	7,427.44	0.262	0.142	4%
FFA20:4	65,459.54	25,719.95	77,761.77	33,507.37	0.060	0.104	19%
FFA20:3	72,590.15	7,563.17	71,680.63	4,878.05	0.507	0.762	-1%
FFA18:3	21,879.83	4,642.97	19,572.84	2,213.94	0.004	0.023	-11%
FFA18:2	825,883.82	287,515.05	761,451.75	216,593.93	0.242	0.407	-8%
FFA18:1	382,384.30	78,245.13	339,748.69	59,301.88	0.005	0.007	-11%
FFA18:0	2,545,189.69	172,275.66	2,398,760.76	250,820.40	0.002	0.004	-6%
FFA16:1	1,000,727.24	245,056.04	769,717.65	250,768.36	0.000	0.000	-23%
FFA16:0	2,689,712.49	204,045.72	2,625,052.78	217,529.74	0.159	0.106	-2%
FFA14:0	232,674.32	19,646.13	227,209.14	21,555.62	0.223	0.325	-2%
FA13:0	1,365,213.91	169,640.88	1,407,736.41	181,208.14	0.265	0.131	3%
FA12:0	1,519,191.44	201,698.34	1,614,912.05	210,845.36	0.034	0.016	6%
SM d18:1/16:1	25,301.54	13,156.13	52,620.85	71,195.78	0.017	0.002	108%
SM d18:1/16:0	175,643.25	91,966.50	514,030.24	812,355.35	0.009	0.000	193%
SM d18:0/16:0	19,142.55	10,433.59	52,340.65	85,042.84	0.014	0.000	173%
SM d18:1/17:1	491.95	303.25	1,422.02	2,098.66	0.006	0.000	189%
SM d18:1/17:0	3,208.37	1,806.82	9,836.29	15,034.51	0.006	0.000	207%
SM d18:1/18:1	18,640.25	9,808.52	43,836.62	65,728.79	0.016	0.001	135%
SM d18:1/18:0	40,892.78	20,053.25	90,535.08	135,225.95	0.021	0.002	121%
SM d18:0/18:0	6,790.95	4,093.27	10,526.87	14,699.17	0.116	0.452	55%
SM d18:1/19:1	447.89	234.09	1,460.18	2,219.10	0.004	0.000	226%
SM d18:1/19:0	1,787.55	822.65	4,662.20	6,747.23	0.007	0.000	161%
SM d18:1/20:1	8,343.49	4,449.21	24,634.38	36,978.63	0.006	0.000	195%
SM d18:1/20:0	25,222.21	11,121.24	62,633.45	95,752.40	0.014	0.000	148%
SM d18:1/21:1	1,046.96	466.41	2,833.69	3,938.79	0.004	0.000	171%
SM d18:1/21:0	5,055.41	2,199.41	13,027.86	19,640.68	0.011	0.000	158%
SM d18:1/22:1	31,914.57	14,523.51	88,831.88	133,223.32	0.007	0.000	178%
SM d18:1/22:0	52,701.82	23,465.98	129,288.92	189,096.71	0.011	0.000	145%
SM d18:1/23:1	11,568.81	4,957.16	35,011.67	50,500.29	0.004	0.000	203%
SM d18:1/23:0	18,495.56	8,310.51	46,935.02	65,107.29	0.006	0.000	154%
SM d18:1/24:1	106,811.38	40,160.09	263,648.05	356,332.79	0.006	0.000	147%
SM d18:1/24:0	44,159.97	18,958.22	108,004.11	149,031.73	0.007	0.000	145%
SM d18:0/24:0	4,760.18	2,080.05	10,957.67	14,970.47	0.009	0.000	130%
SM d18:1/25:1	2,455.32	955.44	6,022.50	7,390.92	0.003	0.000	145%
SM d18:1/25:0	1,984.13	790.49	5,076.28	6,684.72	0.004	0.000	156%
SM d18:0/25:0	1,065.26	393.11	3,199.24	4,379.92	0.002	0.000	200%
SM d18:1/26:1	688.89	294.16	1,769.72	2,118.06	0.002	0.000	157%
SM d18:1/26:0	331.54	179.75	917.12	955.55	0.000	0.000	177%
SM d18:0/26:0	131.90	63.94	420.75	433.64	0.000	0.000	219%
Cer d18:1/16:0	728.41	354.42	728.69	250.48	0.997	0.369	0%
Cer d18:1/18:0	411.52	368.97	372.52	216.29	0.549	0.876	-9%
Cer d18:0/18:0	243.21	242.38	259.16	193.09	0.736	0.204	7%
Cer d18:1/20:0	363.41	428.94	271.26	163.99	0.188	0.442	-25%
Cer d18:1/22:0	1,109.08	461.70	952.66	482.30	0.129	0.045	-14%
Cer d18:1/24:1	2,579.23	1,670.39	1,871.32	911.86	0.016	0.009	-27%
Cer d18:1/24:0	3,348.22	1,577.30	2,789.03	1,280.18	0.074	0.037	-17%
Cer d18:0/24:1	211.93	188.27	212.47	160.36	0.988	0.447	0%

GluCer d18:1/16:0	743.11	288.65	769.57	264.47	0.658	0.557	4%
GluCer d18:0/16:0	27.51	9.87	26.66	8.26	0.666	0.853	-3%
GluCer d18:1/18:0	98.66	35.95	107.11	42.88	0.326	0.471	9%
GluCer d18:0/18:0	7.15	3.44	7.91	3.75	0.334	0.548	11%
GluCer d18:1/20:0	79.67	29.19	97.02	31.86	0.010	0.012	22%
GluCer d18:0/20:0	6.16	2.88	6.77	3.86	0.408	0.598	10%
GluCer d18:1/22:0	673.39	265.07	782.15	306.00	0.082	0.079	16%
GluCer d18:0/22:0	17.83	8.13	18.71	7.42	0.603	0.500	5%
GluCer d18:1/24:1	911.17	286.78	1,004.74	306.84	0.148	0.135	10%
GluCer d18:0/24:1	876.34	374.31	995.37	407.05	0.162	0.128	14%
GluCer d18:1/24:0	25.54	10.59	28.49	11.46	0.219	0.145	12%
GluCer d18:0/24:0	20.89	8.47	22.80	10.31	0.350	0.397	9%
LacCer d18:1/16:0	3,241.04	973.12	3,270.18	986.25	0.891	1.000	1%
LacCer d18:0/16:0	78.43	21.02	76.41	24.58	0.683	0.487	-3%
LacCer d18:1/18:0	100.36	33.07	101.51	64.52	0.918	0.560	1%
LacCer d18:1/20:0	42.51	17.91	40.27	23.77	0.624	0.280	-5%
LacCer d18:1/22:0	171.49	62.64	185.52	105.15	0.457	0.966	8%
LacCer d18:1/24:1	625.25	231.64	670.53	239.75	0.376	0.402	7%
LacCer d18:1/24:0	249.44	90.21	283.84	145.54	0.194	0.427	14%
LacCer d18:0/24:1	16.56	8.50	18.02	6.79	0.382	0.175	9%
Gb3 d18:1/16:0	1,413.50	368.06	1,453.47	335.65	0.600	0.233	3%
Gb3 d18:1/18:0	155.48	52.51	173.19	54.54	0.129	0.134	11%
Gb3 d18:1/20:0	66.58	26.62	72.58	24.25	0.278	0.251	9%
Gb3 d18:1/22:0	207.11	75.27	224.80	74.66	0.277	0.312	9%
Gb3 d18:1/24:1	28.47	16.65	24.78	12.29	0.244	0.557	-13%
Gb3 d18:1/24:0	70.76	27.77	88.15	30.02	0.007	0.002	25%
GM3 d18:1/16:0	3,465.41	967.06	3,231.81	767.81	0.217	0.333	-7%
GM3 d18:0/16:0	744.81	204.69	664.61	172.39	0.052	0.049	-11%
GM3 d18:1/18:1	386.54	116.55	359.59	125.75	0.306	0.213	-7%
GM3 d18:1/18:0	1,531.53	398.74	1,315.67	402.21	0.014	0.004	-14%
GM3 d18:0/18:0	577.43	144.19	491.82	114.25	0.003	0.003	-15%
GM3 d18:1/20:1	200.15	64.44	183.06	69.09	0.240	0.126	-9%
GM3 d18:1/20:0	704.50	243.43	583.90	194.15	0.013	0.018	-17%
GM3 d18:0/20:0	205.34	79.19	154.17	51.27	0.001	0.001	-25%
GM3 d18:1/22:1	888.84	260.81	812.60	253.38	0.173	0.152	-9%
GM3 d18:1/22:0	1,980.84	679.39	1,696.60	555.08	0.036	0.024	-14%
GM3 d18:0/22:0	574.80	225.67	421.35	174.14	0.001	0.000	-27%
GM3 d18:1/24:1	2,471.21	795.58	2,384.20	759.93	0.605	0.691	-4%
GM3 d18:1/24:0	1,837.56	583.45	1,768.44	527.24	0.566	0.500	-4%
GM3 d18:0/24:0	522.42	137.40	422.84	119.75	0.001	0.001	-19%
FFA	10,867,348.82	882,985.02	10,460,387.14	918,832.05	0.039	0.052	-4%
SM	609,084.46	270,992.42	1,584,483.26	2,339,287.65	0.009	0.000	160%
Cer	8,995.02	3,992.95	7,457.11	2,531.94	0.035	0.017	-17%
GluCer	3,487.42	1,227.31	3,867.30	1,317.24	0.171	0.126	11%
LacCer	4,525.08	1,327.02	4,646.27	1,458.56	0.688	0.863	3%
GM3	16,091.36	4,163.69	14,490.66	3,701.17	0.063	0.048	-10%
Gb3	1,941.90	493.99	2,036.97	473.61	0.365	0.120	5%
SM/Cer	71.68	32.29	219.40	312.15	0.003	0.000	206%

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726 **Supplementary Table 5** FPIR differences in individual lipid species

Sphingolipid	FPIR<350 (n=32)		FPIR>350 (n=54)		P value		Percentage changed in FPIR
	Average lipid concentration (nM)	Standard deviation	Average lipid concentration (nM)	Standard deviation	t.test	Man whitney u test	
FFA22:6	30933.36	10802.90	26115.65	10581.45	0.764	0.009	-16%
FFA22:5	37292.94	4346.40	33589.23	6014.57	0.151	0.000	-10%
FFA22:4	46413.66	4107.59	45503.00	5288.10	0.305	0.201	-2%
FFA20:5	38365.22	7441.80	37622.47	6354.22	0.737	0.636	-2%
FFA20:4	72213.60	24411.97	71481.17	33693.18	0.106	0.093	-1%
FFA20:3	73346.37	5041.58	71400.93	6898.52	0.109	0.124	-3%
FFA18:3	21277.51	3718.62	20356.99	3794.93	0.745	0.088	-4%
FFA18:2	897119.34	235720.26	731169.97	246480.70	0.806	0.000	-18%
FFA18:1	397139.23	63927.86	338900.51	68191.46	0.677	0.000	-15%
FFA18:0	2539078.10	174963.97	2429498.92	245429.58	0.005	0.037	-4%
FFA16:1	907304.82	261234.17	867858.64	280367.87	0.471	0.348	-4%
FFA16:0	2735074.86	189190.91	2610145.40	213170.04	0.750	0.001	-5%
FFA14:0	231556.10	18307.13	228883.85	22111.71	0.124	0.761	-1%
FA13:0	1392401.95	127368.27	1383750.44	200297.49	0.013	0.900	-1%
FA12:0	1545982.45	151439.78	1581309.86	239513.03	0.022	0.163	2%
SM d18:1/16:1	28592.38	14527.93	45611.58	65693.88	0.019	0.567	60%
SM d18:1/16:0	220911.63	140418.89	424540.27	749081.64	0.017	0.344	92%
SM d18:0/16:0	22923.05	12621.92	43952.56	78344.84	0.017	0.475	92%
SM d18:1/17:1	609.42	405.39	1180.17	1943.09	0.012	0.235	94%
SM d18:1/17:0	4199.35	2892.12	8021.65	13902.99	0.017	0.304	91%
SM d18:1/18:1	21177.75	10539.15	37666.93	60571.47	0.011	0.555	78%
SM d18:1/18:0	46927.91	21311.30	77765.70	124578.97	0.016	0.971	66%
SM d18:0/18:0	7123.20	3194.99	9638.14	13621.68	0.023	0.284	35%
SM d18:1/19:1	561.22	403.34	1205.56	2049.53	0.012	0.043	115%
SM d18:1/19:0	2215.56	1298.20	3876.22	6227.21	0.018	0.491	75%
SM d18:1/20:1	10106.24	6944.83	20572.95	34096.73	0.012	0.051	104%
SM d18:1/20:0	29256.41	15003.03	53314.81	88037.81	0.017	0.280	82%
SM d18:1/21:1	1249.56	761.24	2382.75	3636.45	0.013	0.093	91%
SM d18:1/21:0	6145.86	3652.73	10905.28	18058.02	0.026	0.296	77%
SM d18:1/22:1	38397.92	25186.68	74449.64	122525.63	0.024	0.035	94%
SM d18:1/22:0	61899.83	35014.45	109655.45	173877.17	0.029	0.136	77%
SM d18:1/23:1	14967.10	11338.97	28656.60	46526.03	0.025	0.062	91%
SM d18:1/23:0	22748.17	14122.38	39148.39	60015.67	0.031	0.195	72%
SM d18:1/24:1	124436.27	64619.26	224159.84	328669.90	0.023	0.064	80%
SM d18:1/24:0	52357.79	29191.84	91323.15	137391.44	0.035	0.120	74%
SM d18:0/24:0	5631.16	3078.11	9293.85	13788.43	0.045	0.218	65%
SM d18:1/25:1	2932.18	1577.39	5079.33	6854.28	0.016	0.074	73%
SM d18:1/25:0	2412.81	1357.12	4249.62	6185.30	0.019	0.110	76%
SM d18:0/25:0	1406.07	927.20	2602.09	4060.15	0.023	0.068	85%
SM d18:1/26:1	848.64	474.83	1474.90	1974.77	0.025	0.095	74%
SM d18:1/26:0	450.29	362.28	738.31	892.52	0.037	0.054	64%
SM d18:0/26:0	196.95	173.68	328.71	406.61	0.041	0.046	67%
Cer d18:1/16:0	770.11	318.55	703.93	295.06	0.365	0.442	-9%
Cer d18:1/18:0	402.53	372.72	385.07	250.03	0.728	1.000	-4%
Cer d18:0/18:0	225.15	189.60	266.91	232.62	0.505	0.348	19%
Cer d18:1/20:0	376.14	475.69	280.78	178.31	0.068	0.543	-25%
Cer d18:1/22:0	1228.05	575.67	911.13	362.82	0.024	0.006	-26%
Cer d18:1/24:1	2712.80	1758.19	1923.27	995.91	0.051	0.007	-29%
Cer d18:1/24:0	3687.60	1795.29	2691.46	1058.12	0.043	0.002	-27%
Cer d18:0/24:1	224.58	194.17	204.87	161.51	0.239	0.782	-9%

GluCer d18:1/16:0	834.39	295.06	710.58	254.47	0.113	0.033	-15%
GluCer d18:0/16:0	27.16	9.33	27.02	8.95	0.718	0.865	0%
GluCer d18:1/18:0	108.75	35.64	99.57	41.78	0.875	0.109	-8%
GluCer d18:0/18:0	7.27	3.66	7.70	3.59	0.334	0.506	6%
GluCer d18:1/20:0	92.66	33.03	86.11	30.83	0.612	0.353	-7%
GluCer d18:0/20:0	6.42	3.19	6.50	3.56	0.793	0.964	1%
GluCer d18:1/22:0	762.16	302.54	709.41	283.78	0.350	0.427	-7%
GluCer d18:0/22:0	17.55	7.97	18.71	7.65	0.989	0.458	7%
GluCer d18:1/24:1	983.05	312.80	944.82	292.86	0.718	0.491	-4%
GluCer d18:0/24:1	1003.47	420.78	897.99	375.21	0.178	0.272	-11%
GluCer d18:1/24:0	27.12	10.58	27.01	11.46	0.914	0.872	0%
GluCer d18:0/24:0	23.09	8.77	21.14	9.83	0.915	0.240	-8%
LacCer d18:1/16:0	3512.77	975.36	3103.76	949.85	0.796	0.047	-12%
LacCer d18:0/16:0	82.38	20.05	74.44	23.97	0.342	0.053	-10%
LacCer d18:1/18:0	113.33	74.54	93.61	28.74	0.044	0.195	-17%
LacCer d18:1/20:0	51.35	27.61	35.45	12.91	0.003	0.003	-31%
LacCer d18:1/22:0	219.30	118.64	154.59	47.60	0.000	0.008	-30%
LacCer d18:1/24:1	722.00	282.60	604.81	192.50	0.010	0.080	-16%
LacCer d18:1/24:0	321.65	165.22	234.67	71.61	0.000	0.007	-27%
LacCer d18:0/24:1	18.57	8.54	16.56	7.07	0.187	0.255	-11%
Gb3 d18:1/16:0	1507.19	393.94	1390.55	317.68	0.489	0.057	-8%
Gb3 d18:1/18:0	169.87	61.39	161.38	49.42	0.290	0.721	-5%
Gb3 d18:1/20:0	70.80	27.65	68.97	24.33	0.485	0.796	-3%
Gb3 d18:1/22:0	221.33	74.61	213.10	75.83	0.860	0.543	-4%
Gb3 d18:1/24:1	27.09	16.33	26.28	13.64	0.191	0.886	-3%
Gb3 d18:1/24:0	79.64	35.20	79.66	26.94	0.127	0.837	0%
GM3 d18:1/16:0	3513.20	950.06	3246.75	817.94	0.349	0.070	-8%
GM3 d18:0/16:0	762.83	190.85	668.78	185.67	0.568	0.013	-12%
GM3 d18:1/18:1	396.85	125.27	358.48	117.88	0.296	0.071	-10%
GM3 d18:1/18:0	1535.46	415.03	1353.32	399.76	0.473	0.022	-12%
GM3 d18:0/18:0	572.90	151.58	510.36	121.33	0.112	0.073	-11%
GM3 d18:1/20:1	194.77	55.15	189.41	73.57	0.312	0.353	-3%
GM3 d18:1/20:0	710.84	259.53	602.48	196.14	0.065	0.076	-15%
GM3 d18:0/20:0	204.08	79.28	164.39	61.42	0.034	0.014	-19%
GM3 d18:1/22:1	906.98	277.97	815.97	242.35	0.591	0.063	-10%
GM3 d18:1/22:0	2038.86	729.71	1714.86	537.18	0.113	0.041	-16%
GM3 d18:0/22:0	568.51	238.55	453.49	187.74	0.341	0.011	-20%
GM3 d18:1/24:1	2582.12	800.58	2334.58	750.43	0.509	0.158	-10%
GM3 d18:1/24:0	1967.27	574.02	1704.37	521.42	0.508	0.024	-13%
GM3 d18:0/24:0	530.96	148.20	436.23	118.36	0.223	0.002	-18%
FFA	10965635.23	805437.08	10477506.62	940992.26	0.305	0.013	-4%
SM	730684.69	410181.86	1331794.46	2155670.38	0.019	0.198	82%
Cer	9626.95	4404.06	7367.43	2283.34	0.030	0.003	-23%
GluCer	3893.08	1366.10	3556.56	1223.52	0.142	0.245	-9%
LacCer	5041.34	1538.19	4317.89	1229.60	0.101	0.029	-14%
GM3	16485.62	4372.49	14553.45	3600.83	0.154	0.039	-12%
Gb3	2075.91	549.72	1939.95	436.65	0.463	0.153	-7%
SM/Cer	78.81	35.76	187.82	288.88	0.005	0.002	138%

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731 **Supplementary Table 6** Pearson's relationship between lipids and clinical characteristics adjusted
732 by age, sex, BMI, TG, TC, HDLc, LDLc, ALT and AST.

lipid	GIR		GIR(age, sex)		GIR(age,sex,LDLc,HDLc,TC,TG)		GIR(age,sex,LDLc,HDLc,TC,TG,BMI)		GIR(age,sex,LDLc,HDLc,TC,TG,BMI,AS T,ALT)	
	r	p	adjusted r	p	adjusted r	p	adjusted r	p	adjusted r	p
FFA22:6	0.111	0.308	0.140	0.034	0.238	0.034	0.274	0.015	0.266	0.019
FFA22:5	-0.138	0.204	-0.079	0.103	0.184	0.103	0.259	0.021	0.247	0.031
FFA22:4	-.242*	0.025	-0.202	0.871	-0.019	0.871	0.118	0.300	0.078	0.501
FFA20:5	0.131	0.230	0.126	0.292	0.119	0.292	0.270	0.016	0.245	0.031
FFA20:4	.304**	0.004	0.304	0.001	0.360	0.001	0.455	0.000	0.428	0.000
FFA20:3	-0.066	0.544	-0.024	0.524	0.072	0.524	0.162	0.154	0.138	0.230
FFA18:3	-.287**	0.007	-0.242	0.717	-0.041	0.717	0.062	0.588	0.045	0.695
FFA18:2	-0.186	0.087	-0.123	0.544	0.069	0.544	0.190	0.093	0.164	0.154
FFA18:1	-.384**	0.000	-0.340	0.370	-0.102	0.370	0.008	0.942	0.002	0.987
FFA18:0	-.498**	0.000	-0.495	0.009	-0.291	0.009	-0.176	0.120	-0.185	0.108
FFA16:1	-.555**	0.000	-0.548	0.000	-0.396	0.000	-0.214	0.058	-0.243	0.033
FFA16:0	-.294**	0.006	-0.283	0.506	-0.076	0.506	0.028	0.807	0.007	0.952
FFA14:0	-0.207	0.056	-0.182	0.656	-0.051	0.656	0.050	0.660	0.019	0.869
FA13:0	0.151	0.166	0.172	0.294	0.119	0.294	0.093	0.414	0.077	0.504
FA12:0	.239*	0.027	0.250	0.270	0.125	0.270	0.066	0.564	0.037	0.748
SM d18:1/16:1	.441**	0.000	0.420	0.000	0.403	0.000	0.313	0.005	0.317	0.005
SM d18:1/16:0	.468**	0.000	0.449	0.000	0.422	0.000	0.319	0.004	0.323	0.004
SM d18:0/16:0	.442**	0.000	0.422	0.000	0.405	0.000	0.304	0.007	0.308	0.006
SM d18:1/17:1	.483**	0.000	0.466	0.000	0.430	0.000	0.325	0.003	0.330	0.003
SM d18:1/17:0	.482**	0.000	0.466	0.000	0.432	0.000	0.322	0.004	0.328	0.004
SM d18:1/18:1	.435**	0.000	0.416	0.000	0.400	0.000	0.293	0.009	0.298	0.008
SM d18:1/18:0	.424**	0.000	0.405	0.000	0.392	0.000	0.287	0.010	0.294	0.009
SM d18:0/18:0	.323**	0.002	0.300	0.003	0.328	0.003	0.239	0.034	0.250	0.028
SM d18:1/19:1	.495**	0.000	0.477	0.000	0.439	0.000	0.330	0.003	0.333	0.003
SM d18:1/19:0	.469**	0.000	0.456	0.000	0.424	0.000	0.317	0.004	0.325	0.004
SM d18:1/20:1	.484**	0.000	0.466	0.000	0.432	0.000	0.326	0.003	0.330	0.003
SM d18:1/20:0	.444**	0.000	0.428	0.000	0.410	0.000	0.305	0.006	0.311	0.006
SM d18:1/21:1	.494**	0.000	0.477	0.000	0.449	0.000	0.345	0.002	0.347	0.002
SM d18:1/21:0	.463**	0.000	0.449	0.000	0.427	0.000	0.328	0.003	0.335	0.003
SM d18:1/22:1	.479**	0.000	0.461	0.000	0.431	0.000	0.333	0.003	0.337	0.003
SM d18:1/22:0	.463**	0.000	0.445	0.000	0.424	0.000	0.329	0.003	0.332	0.003
SM d18:1/23:1	.512**	0.000	0.495	0.000	0.462	0.000	0.359	0.001	0.363	0.001
SM d18:1/23:0	.492**	0.000	0.477	0.000	0.450	0.000	0.355	0.001	0.359	0.001
SM d18:1/24:1	.473**	0.000	0.458	0.000	0.438	0.000	0.338	0.002	0.339	0.003
SM d18:1/24:0	.474**	0.000	0.458	0.000	0.431	0.000	0.340	0.002	0.345	0.002
SM d18:0/24:0	.464**	0.000	0.449	0.000	0.428	0.000	0.340	0.002	0.346	0.002
SM d18:1/25:1	.507**	0.000	0.495	0.000	0.446	0.000	0.343	0.002	0.351	0.002
SM d18:1/25:0	.506**	0.000	0.491	0.000	0.447	0.000	0.343	0.002	0.349	0.002
SM d18:0/25:0	.519**	0.000	0.503	0.000	0.460	0.000	0.353	0.001	0.354	0.002
SM d18:1/26:1	.514**	0.000	0.502	0.000	0.464	0.000	0.368	0.001	0.368	0.001
SM d18:1/26:0	.587**	0.000	0.571	0.000	0.507	0.000	0.431	0.000	0.429	0.000
SM d18:0/26:0	.642**	0.000	0.628	0.000	0.552	0.000	0.463	0.000	0.463	0.000
Cer d18:1/16:0	0.041	0.707	0.043	0.996	-0.001	0.996	0.004	0.972	-0.001	0.994
Cer d18:1/18:0	-0.062	0.571	-0.082	0.411	-0.093	0.411	0.111	0.331	0.073	0.526
Cer d18:0/18:0	0.016	0.886	0.008	0.735	0.038	0.735	0.028	0.809	0.024	0.837
Cer d18:1/20:0	-0.145	0.184	-0.147	0.653	-0.051	0.653	0.141	0.216	0.128	0.269
Cer d18:1/22:0	-0.195	0.071	-0.194	0.998	0.000	0.998	-0.033	0.771	-0.022	0.853
Cer d18:1/24:1	-.263*	0.014	-0.247	0.370	-0.102	0.370	0.021	0.853	0.003	0.982
Cer d18:1/24:0	-0.186	0.087	-0.150	0.614	0.057	0.614	-0.005	0.967	0.018	0.875
Cer d18:0/24:1	0.028	0.796	0.034	0.863	0.020	0.863	0.086	0.450	0.065	0.576

GluCer d18:1/16:0	0.056	0.608	0.030	0.126	0.172	0.126	0.121	0.287	0.145	0.209
GluCer d18:0/16:0	0.009	0.936	-0.005	0.404	0.095	0.404	0.113	0.322	0.112	0.332
GluCer d18:1/18:0	0.095	0.384	0.087	0.164	0.157	0.164	0.005	0.967	0.018	0.877
GluCer d18:0/18:0	0.105	0.337	0.064	0.073	0.202	0.073	0.037	0.744	0.086	0.458
GluCer d18:1/20:0	.262*	0.015	0.253	0.006	0.302	0.006	0.164	0.150	0.169	0.141
GluCer d18:0/20:0	0.057	0.604	0.046	0.835	0.024	0.835	0.068	0.554	0.043	0.714
GluCer d18:1/22:0	.233*	0.031	0.219	0.001	0.365	0.001	0.241	0.032	0.237	0.038
GluCer d18:0/22:0	0.145	0.182	0.107	0.143	0.165	0.143	0.101	0.375	0.072	0.535
GluCer d18:1/24:1	0.186	0.086	0.153	0.012	0.280	0.012	0.211	0.063	0.196	0.087
GluCer d18:0/24:1	0.169	0.121	0.163	0.006	0.307	0.006	0.226	0.045	0.229	0.045
GluCer d18:1/24:0	0.195	0.071	0.170	0.004	0.321	0.004	0.242	0.031	0.236	0.039
GluCer d18:0/24:0	0.115	0.293	0.081	0.130	0.171	0.130	0.197	0.081	0.190	0.098
LacCer d18:1/16:0	0.046	0.675	0.071	0.230	0.136	0.230	0.112	0.325	0.130	0.259
LacCer d18:0/16:0	-0.012	0.909	0.001	0.731	-0.039	0.731	0.013	0.909	0.025	0.829
LacCer d18:1/18:0	0.185	0.089	0.198	0.385	0.099	0.385	0.101	0.378	0.125	0.278
LacCer d18:1/20:0	-0.023	0.834	-0.033	0.649	-0.052	0.649	-0.073	0.524	-0.035	0.759
LacCer d18:1/22:0	0.143	0.190	0.163	0.110	0.180	0.110	0.141	0.215	0.163	0.156
LacCer d18:1/24:1	0.180	0.097	0.183	0.328	0.111	0.328	0.061	0.596	0.087	0.450
LacCer d18:1/24:0	.239*	0.027	0.259	0.115	0.178	0.115	0.151	0.185	0.200	0.081
LacCer d18:0/24:1	0.094	0.387	0.129	0.283	0.121	0.283	-0.015	0.896	-0.021	0.855
Gb3 d18:1/16:0	0.193	0.075	0.193	0.036	0.235	0.036	0.277	0.013	0.256	0.025
Gb3 d18:1/18:0	.267*	0.013	0.288	0.019	0.261	0.019	0.122	0.283	0.070	0.542
Gb3 d18:1/20:0	0.164	0.131	0.164	0.358	0.104	0.358	0.045	0.695	0.051	0.657
Gb3 d18:1/22:0	.285**	0.008	0.290	0.045	0.225	0.045	0.252	0.025	0.219	0.055
Gb3 d18:1/24:1	0.033	0.766	0.004	0.858	0.020	0.858	0.061	0.592	0.041	0.725
Gb3 d18:1/24:0	.351**	0.001	0.363	0.030	0.243	0.030	0.270	0.016	0.264	0.020
GM3 d18:1/16:0	-0.157	0.148	-0.148	0.986	-0.002	0.986	-0.054	0.634	-0.001	0.996
GM3 d18:0/16:0	-.244*	0.023	-0.209	0.580	-0.063	0.580	-0.076	0.507	-0.022	0.849
GM3 d18:1/18:1	-0.120	0.272	-0.105	0.224	-0.138	0.224	-0.189	0.095	-0.166	0.150
GM3 d18:1/18:0	-.312**	0.003	-0.280	0.027	-0.247	0.027	-0.284	0.011	-0.243	0.033
GM3 d18:0/18:0	-.422**	0.000	-0.397	0.002	-0.345	0.002	-0.344	0.002	-0.290	0.011
GM3 d18:1/20:1	-.247*	0.022	-0.228	0.104	-0.183	0.104	-0.201	0.076	-0.210	0.066
GM3 d18:1/20:0	-.431**	0.000	-0.393	0.017	-0.266	0.017	-0.295	0.008	-0.235	0.039
GM3 d18:0/20:0	-.507**	0.000	-0.490	0.000	-0.383	0.000	-0.350	0.002	-0.306	0.007
GM3 d18:1/22:1	-.280**	0.009	-0.261	0.334	-0.109	0.334	-0.117	0.304	-0.064	0.579
GM3 d18:1/22:0	-.347**	0.001	-0.316	0.369	-0.102	0.369	-0.132	0.246	-0.070	0.546
GM3 d18:0/22:0	-.471**	0.000	-0.446	0.072	-0.203	0.072	-0.235	0.037	-0.172	0.135
GM3 d18:1/24:1	-0.180	0.097	-0.150	0.542	-0.069	0.542	-0.199	0.079	-0.140	0.223
GM3 d18:1/24:0	-0.147	0.178	-0.106	0.942	-0.008	0.942	-0.118	0.299	-0.049	0.670
GM3 d18:0/24:0	-.400**	0.000	-0.377	0.111	-0.179	0.111	-0.165	0.146	-0.115	0.317
FFA	-.350**	0.001	-0.316	0.284	-0.121	0.284	0.021	0.855	-0.015	0.894
SM	.467**	0.000	0.449	0.000	0.425	0.000	0.324	0.004	0.328	0.004
Cer	-.227*	0.036	-0.205	0.786	-0.031	0.786	0.039	0.735	0.035	0.765
GluCer	0.173	0.111	0.153	0.006	0.304	0.006	0.213	0.060	0.214	0.061
LacCer	0.099	0.362	0.122	0.201	0.144	0.201	0.114	0.316	0.139	0.228
GM3	-.301**	0.005	-0.270	0.252	-0.130	0.252	-0.200	0.078	-0.134	0.247
Gb3	.245*	0.023	0.248	0.016	0.268	0.016	0.287	0.010	0.260	0.022
SM/Cer	.498**	0.000	0.478	0.000	0.434	0.000	0.318	0.004	0.321	0.004

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737 Supplementary Table 7 ROC curve for insulin sensitivity.

lipid	FPIR		FPIR(age, sex)		FPIR(age,sex,LDLc,HDLc,TC,TG)		FPIR(age,sex,LDLc,HDLc,TC,TG,BMI)		FPIR(age,sex,LDLc,HDLc,TC,TG,BMI,AS T,ALT)	
	r	p	adjusted r	p	adjusted r	p	adjusted r	p	adjusted r	p
FFA22:6	-.216*	0.046	-0.180	0.131	-0.170	0.131	-0.176	0.12	-0.196	0.088
FFA22:5	-.300**	0.005	-0.233	0.032	-0.240	0.032	-0.239	0.034	-0.266	0.019
FFA22:4	-0.199	0.067	-0.164	0.096	-0.187	0.096	-0.172	0.129	-0.218	0.057
FFA20:5	-0.158	0.146	-0.196	0.088	-0.192	0.088	-0.18	0.113	-0.217	0.058
FFA20:4	-0.164	0.132	-0.180	0.119	-0.176	0.119	-0.179	0.115	-0.231	0.043
FFA20:3	-0.195	0.072	-0.162	0.147	-0.164	0.147	-0.156	0.169	-0.192	0.094
FFA18:3	-0.062	0.571	0.001	0.987	0.002	0.987	0.017	0.881	0.004	0.973
FFA18:2	-.295**	0.006	-0.235	0.037	-0.234	0.037	-0.224	0.047	-0.259	0.023
FFA18:1	-.314**	0.003	-0.248	0.014	-0.273	0.014	-0.26	0.021	-0.272	0.017
FFA18:0	-0.197	0.069	-0.143	0.101	-0.185	0.101	-0.163	0.15	-0.173	0.132
FFA16:1	0.034	0.758	0.066	0.568	0.065	0.568	0.116	0.31	0.103	0.372
FFA16:0	-.306**	0.004	-0.278	0.007	-0.302	0.007	-0.29	0.009	-0.322	0.004
FFA14:0	-0.056	0.607	-0.027	0.736	-0.038	0.736	-0.024	0.837	-0.054	0.64
FA13:0	-0.03	0.781	-0.013	0.903	-0.014	0.903	-0.022	0.847	-0.043	0.711
FA12:0	0.022	0.843	0.026	0.800	0.029	0.800	0.016	0.886	-0.013	0.913
SM d18:1/16:1	-0.037	0.734	-0.075	0.591	-0.061	0.591	-0.094	0.41	-0.099	0.391
SM d18:1/16:0	-0.028	0.8	-0.065	0.643	-0.053	0.643	-0.089	0.435	-0.094	0.415
SM d18:0/16:0	-0.026	0.814	-0.062	0.652	-0.051	0.652	-0.086	0.451	-0.091	0.433
SM d18:1/17:1	-0.029	0.792	-0.062	0.680	-0.047	0.680	-0.084	0.463	-0.089	0.443
SM d18:1/17:0	-0.029	0.79	-0.063	0.668	-0.049	0.668	-0.087	0.446	-0.091	0.431
SM d18:1/18:1	-0.035	0.747	-0.068	0.634	-0.054	0.634	-0.09	0.431	-0.093	0.423
SM d18:1/18:0	-0.034	0.755	-0.067	0.633	-0.054	0.633	-0.089	0.435	-0.091	0.434
SM d18:0/18:0	-0.043	0.695	-0.076	0.546	-0.068	0.546	-0.097	0.394	-0.093	0.423
SM d18:1/19:1	-0.022	0.838	-0.058	0.707	-0.043	0.707	-0.081	0.479	-0.087	0.452
SM d18:1/19:0	-0.028	0.796	-0.055	0.724	-0.040	0.724	-0.077	0.502	-0.078	0.503
SM d18:1/20:1	-0.021	0.847	-0.056	0.718	-0.041	0.718	-0.078	0.494	-0.083	0.472
SM d18:1/20:0	-0.015	0.89	-0.045	0.790	-0.030	0.790	-0.065	0.569	-0.067	0.562
SM d18:1/21:1	-0.017	0.88	-0.049	0.776	-0.032	0.776	-0.07	0.542	-0.077	0.507
SM d18:1/21:0	-0.01	0.93	-0.038	0.852	-0.021	0.852	-0.055	0.628	-0.056	0.626
SM d18:1/22:1	-0.01	0.93	-0.045	0.792	-0.030	0.792	-0.065	0.57	-0.069	0.549
SM d18:1/22:0	-0.012	0.912	-0.049	0.759	-0.035	0.759	-0.069	0.546	-0.074	0.523
SM d18:1/23:1	-0.019	0.863	-0.054	0.737	-0.038	0.737	-0.076	0.504	-0.083	0.475
SM d18:1/23:0	-0.024	0.828	-0.058	0.708	-0.043	0.708	-0.079	0.489	-0.084	0.466
SM d18:1/24:1	-0.024	0.823	-0.058	0.692	-0.045	0.692	-0.081	0.475	-0.092	0.428
SM d18:1/24:0	-0.016	0.882	-0.053	0.727	-0.040	0.727	-0.074	0.518	-0.079	0.497
SM d18:0/24:0	-0.016	0.883	-0.053	0.724	-0.040	0.724	-0.073	0.52	-0.077	0.506
SM d18:1/25:1	-0.026	0.811	-0.056	0.721	-0.041	0.721	-0.078	0.495	-0.08	0.488
SM d18:1/25:0	-0.024	0.824	-0.059	0.695	-0.045	0.695	-0.082	0.471	-0.086	0.455
SM d18:0/25:0	-0.027	0.806	-0.065	0.652	-0.051	0.652	-0.091	0.425	-0.101	0.384
SM d18:1/26:1	-0.033	0.764	-0.064	0.647	-0.052	0.647	-0.09	0.431	-0.102	0.378
SM d18:1/26:0	-0.044	0.69	-0.094	0.457	-0.084	0.457	-0.123	0.28	-0.14	0.224
SM d18:0/26:0	-0.039	0.72	-0.088	0.507	-0.075	0.507	-0.12	0.291	-0.135	0.24
Cer d18:1/16:0	-0.171	0.114	-0.185	0.112	-0.179	0.112	-0.179	0.114	-0.194	0.09
Cer d18:1/18:0	0.047	0.668	-0.004	0.973	0.004	0.973	0.035	0.758	0.004	0.969
Cer d18:0/18:0	0.039	0.719	0.026	0.710	0.042	0.710	0.04	0.729	0.046	0.689
Cer d18:1/20:0	-0.023	0.837	-0.048	0.740	-0.038	0.740	-0.012	0.919	-0.022	0.851
Cer d18:1/22:0	-0.071	0.513	-0.049	0.755	-0.035	0.755	-0.04	0.727	-0.022	0.849
Cer d18:1/24:1	-.213*	0.049	-0.180	0.067	-0.206	0.067	-0.19	0.093	-0.207	0.07
Cer d18:1/24:0	-0.109	0.32	-0.045	0.757	-0.035	0.757	-0.046	0.688	-0.022	0.851
Cer d18:0/24:1	0.024	0.829	0.037	0.637	0.053	0.637	0.062	0.588	0.042	0.715

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GluCer d18:1/16:0	-0.225*	0.038	-0.284	0.001	-0.350	0.001	-0.369	0.001	-0.372	0.001
GluCer d18:0/16:0	-0.092	0.397	-0.130	0.144	-0.165	0.144	-0.167	0.141	-0.179	0.118
GluCer d18:1/18:0	-0.236*	0.029	-0.232	0.013	-0.276	0.013	-0.313	0.005	-0.314	0.005
GluCer d18:0/18:0	0.052	0.637	0.012	0.851	0.021	0.851	-0.009	0.94	0.043	0.711
GluCer d18:1/20:0	-0.255*	0.018	-0.278	0.007	-0.302	0.007	-0.349	0.002	-0.376	0.001
GluCer d18:0/20:0	-0.003	0.979	-0.038	0.726	-0.040	0.726	-0.035	0.758	-0.068	0.558
GluCer d18:1/22:0	-0.152	0.163	-0.202	0.035	-0.236	0.035	-0.282	0.012	-0.309	0.006
GluCer d18:0/22:0	-0.001	0.996	-0.061	0.487	-0.079	0.487	-0.095	0.403	-0.142	0.217
GluCer d18:1/24:1	-0.157	0.149	-0.218	0.024	-0.253	0.024	-0.28	0.012	-0.325	0.004
GluCer d18:0/24:1	-0.137	0.208	-0.181	0.046	-0.223	0.046	-0.254	0.024	-0.271	0.017
GluCer d18:1/24:0	-0.114	0.295	-0.174	0.072	-0.202	0.072	-0.233	0.039	-0.258	0.023
GluCer d18:0/24:0	-0.111	0.307	-0.207	0.027	-0.247	0.027	-0.252	0.025	-0.296	0.009
LacCer d18:1/16:0	-0.172	0.113	-0.158	0.119	-0.176	0.119	-0.186	0.101	-0.172	0.136
LacCer d18:0/16:0	-0.074	0.498	-0.068	0.496	-0.077	0.496	-0.07	0.543	-0.052	0.656
LacCer d18:1/18:0	-0.128	0.242	-0.122	0.293	-0.119	0.293	-0.124	0.278	-0.103	0.375
LacCer d18:1/20:0	-0.256*	0.018	-0.278	0.013	-0.277	0.013	-0.279	0.013	-0.246	0.031
LacCer d18:1/22:0	-0.207	0.056	-0.200	0.078	-0.198	0.078	-0.213	0.06	-0.2	0.081
LacCer d18:1/24:1	-0.234*	0.03	-0.265	0.013	-0.277	0.013	-0.291	0.009	-0.277	0.015
LacCer d18:1/24:0	-0.240*	0.026	-0.232	0.030	-0.243	0.030	-0.256	0.023	-0.224	0.05
LacCer d18:0/24:1	-0.112	0.306	-0.112	0.310	-0.115	0.310	-0.141	0.214	-0.143	0.215
Gb3 d18:1/16:0	-0.194	0.073	-0.204	0.041	-0.229	0.041	-0.234	0.038	-0.277	0.015
Gb3 d18:1/18:0	-0.134	0.22	-0.107	0.397	-0.096	0.397	-0.131	0.251	-0.197	0.086
Gb3 d18:1/20:0	-0.068	0.532	-0.039	0.808	-0.028	0.808	-0.04	0.726	-0.048	0.682
Gb3 d18:1/22:0	-0.045	0.68	-0.028	0.947	-0.008	0.947	-0.013	0.909	-0.063	0.585
Gb3 d18:1/24:1	0.051	0.643	-0.009	0.960	-0.006	0.960	-0.001	0.992	-0.024	0.838
Gb3 d18:1/24:0	-0.057	0.605	-0.071	0.534	-0.071	0.534	-0.077	0.498	-0.092	0.425
GM3 d18:1/16:0	-0.183	0.091	-0.186	0.036	-0.235	0.036	-0.244	0.03	-0.201	0.079
GM3 d18:0/16:0	-0.198	0.068	-0.158	0.092	-0.190	0.092	-0.19	0.093	-0.145	0.207
GM3 d18:1/18:1	-0.126	0.249	-0.129	0.289	-0.120	0.289	-0.122	0.284	-0.108	0.348
GM3 d18:1/18:0	-0.094	0.389	-0.080	0.434	-0.089	0.434	-0.084	0.46	-0.043	0.713
GM3 d18:0/18:0	-0.088	0.421	-0.060	0.516	-0.074	0.516	-0.06	0.597	0.015	0.895
GM3 d18:1/20:1	-0.114	0.297	-0.086	0.502	-0.076	0.502	-0.072	0.53	-0.078	0.498
GM3 d18:1/20:0	-0.109	0.318	-0.051	0.630	-0.055	0.630	-0.048	0.672	0.029	0.805
GM3 d18:0/20:0	-0.073	0.503	-0.046	0.739	-0.038	0.739	-0.018	0.874	0.057	0.623
GM3 d18:1/22:1	-0.209	0.054	-0.195	0.064	-0.208	0.064	-0.206	0.069	-0.166	0.149
GM3 d18:1/22:0	-0.107	0.327	-0.072	0.441	-0.087	0.441	-0.088	0.442	-0.022	0.848
GM3 d18:0/22:0	-0.066	0.547	-0.025	0.698	-0.044	0.698	-0.041	0.722	0.036	0.755
GM3 d18:1/24:1	-0.121	0.266	-0.095	0.347	-0.107	0.347	-0.122	0.283	-0.077	0.508
GM3 d18:1/24:0	-0.104	0.34	-0.086	0.428	-0.090	0.428	-0.105	0.356	-0.04	0.728
GM3 d18:0/24:0	-0.188	0.083	-0.148	0.099	-0.186	0.099	-0.178	0.116	-0.118	0.307
FFA	-0.231*	0.032	-0.173	0.094	-0.189	0.094	-0.17	0.133	-0.21	0.066
SM	-0.024	0.826	-0.060	0.683	-0.046	0.683	-0.082	0.471	-0.088	0.449
Cer	-0.152	0.161	-0.117	0.264	-0.126	0.264	-0.117	0.303	-0.118	0.306
GluCer	-0.177	0.102	-0.231	0.012	-0.281	0.012	-0.316	0.005	-0.34	0.002
LacCer	-0.205	0.058	-0.199	0.054	-0.217	0.054	-0.229	0.043	-0.211	0.066
GM3	-0.154	0.157	-0.130	0.162	-0.158	0.162	-0.163	0.151	-0.101	0.381
Gb3	-0.168	0.121	-0.171	0.087	-0.193	0.087	-0.203	0.073	-0.255	0.025
SM/Cer	-0.004	0.972	-0.044	0.775	-0.032	0.775	-0.071	0.535	-0.078	0.501

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