Supplementary Online Content

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eAppendix 1. Chronology of funding for DIETFITS – increased sample size, additional primary analysis

Overview

This document is intended to summarize the impact on our study when an additional $5M became available in September 2013 to augment the $3.2M from NIH/NIDDK received in August 2012. Main impacts relevant to changes to CT.GOV include:

- Original projected sample size of n=400 was increased to n=600 (actual enrollment was n=609)
- Original population of Caucasian-only was expanded to all races/ethnicities
- An additional primary analysis was incorporated into the main objectives – insulin secretion (INS-30).

1. NIH/NIDDK funding received in 2012 (R01-DK91381, $3.2M, 5 years)

a. Primary endpoint: Weight

b. Primary analysis: Diet Group X Genotype Pattern (2X2); Hypothesis - interaction/effect-modification for 12-month weight loss

c. Original projected sample size: n=400
Existing data used to project 40% Low-Fat Genotype (LFG), 40% Low-Carb Genotype (LCG), and 20% that would be NEITHER LFG or LCG (40:40:20)

> *Note: Primary analysis was designed to focus on the n=320 of the full n=400 (expecting n= ~160 LFG, and n= ~160 LCG). Those falling in the NEITHER group (n= ~80) were to be enrolled and randomized but only included in secondary analyses.*
>
> *Note: NIH recommended that recruitment be limited to Caucasians, focusing on only one ancestry group, due to lack of available/adequate data on allele frequencies in non-Caucasian populations.*

d. Original randomization plan: Conduct genotyping during baseline data collection, stratify randomization to Low-Fat vs. Low-Carb by genotype pattern.

2. Decision to not stratify randomization by genotype pattern. After discussions with several expert colleagues, we decided to ***not stratify randomization based on genotype*** due to the ever-evolving nature of genetic/GWAS studies that might have shown the trial to be obsolete before completion. Randomizing on the initial 3-SNP genotype pattern would limit the use of the rich data set collected as part of the study and the ability to use this to continue investigation into which factors might modify weight loss on these diets. Given the existing data that suggested a ~40:40:20 distribution of LFG, LCG and NEITHER-Genotype, it was anticipated that adequate representation of the two main genotypes – LFG and LCG – would be achieved in both diet groups through straight randomization to the two diet groups, without stratification. Adequate representation would allow for the original 2X2 analysis to be conducted.

3. Approached by the Nutrition Science Initiative (NuSI). In the fall of 2012, just after being funded by NIH, we were approached by the newly founded NuSI group with an extraordinary offer to provide an initial $3M in unrestricted funds to augment the study if we could also raise a matching $2M in unrestricted funds from donors within an 8-month time frame (January 1-August 31, 2013); i.e., a total augmentation of $5M to the initial $3.2 from NIH.

The primary request from NuSI was to make the study more rigorous and more impactful. The specific factors agreed on were to make the study larger (more participants) and more extensive (more secondary and exploratory outcomes measures) without extending the timeline (faster pace of enrollment).

We prioritized:

a. Increasing sample size from n=400 to n=600.

b. Opening inclusion criteria to all race/ethnic groups (projecting that ~2/3 of the 600 would be Caucasian (n=400), and thus not compromising the original plan to recruit 400 Caucasians)

c. Adding a ***second primary effect modifier*** - ***insulin resistance*** (which we chose to assess as insulin secretion, INS–30, as described elsewhere)

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Note: Although we were fairly certain we would eventually receive this generous augmentation to our study funding, at the time the first participants were enrolled in the spring of 2013 we were not 100% certain, and therefore the CT.GOV registration and original IRB protocol had to be submitted assuming the funds available would be only the original $3.2M from NIH, with a sample size of n=400.

Note: This is also the reason that the first 78 participants did not participate in DEXA assessment of % body fat, or Metabolic Cart assessment of 1) Resting Energy Expenditure (REE) or 2) Respiratory Exchange Ratio (RER). Those assessments had been part of the original study design proposed to NIH, but had to be eliminated when our budget was cut 13% across all years. We were able to add those measurements back when the NuSI funds became available in the fall of 2013.

4. Straight randomization to Low-Fat and Low-Carb. Given #2 and #3 above, when the first participants were enrolled in the study, beginning January 29, 2013, there was no stratification of randomization. Participants were randomized using blockrand in R, in blocks of 8, simply to Low-Fat or Low-Carb.

5. Communication/documentation of these changes.
IRB changes were made noting larger sample size and added measurements starting in 2013.
The NIH Project Officer for this grant, Robert Karp, was told of the randomization plan during a visit to Stanford in June 2014, and he expressed concurrence.

On October 12, 2015 we changed the CT.GOV to note that the *primary analyses* would now include a *second effect modifier – insulin resistance*.

In August of 2016 we submitted a Methods and Design manuscript to Contemporary Clinical Trials describing the changes described above (accepted and available on-line in December 2016)

These decisions had been made and were in place prior to unblinding the randomization assignment and prior to doing any of the statistical analyses.

6. Using insulin secretion, rather than a proxy measure of insulin resistance.
In a pilot study for the current DIETFITS study (Gardner et al., Obesity, 2016;24:79-86), we had used INS-AUC (area-under-the-curve of insulin concentrations at 0, 30, 60 and 120 minutes from an Oral Glucose Tolerance Test, OGTT) as a proxy measure of insulin resistance.
We had planned to use the same measure in the main analysis in DIETFITS.
Prior to running any analyses, we discussed different possible related measures available from the OGTT, and it was decided that insulin secretion (INS-30) would be superior.
INS-30 was used in the primary analysis.
This is described in the main part of this paper.

7. SUMMARY

For the reasons described above:

a. Randomization was not stratified – it was a straight randomization to the two diet groups

b. With n=600, the study was adequately powered to test two distinct potential effect modifiers – INS-30 and Genotype Pattern.

c. % Body Fat, REE and RER are missing at baseline for ~n=80 participants due to the events described above.

This can be challenging to communicate efficiently in the main manuscript. The original NIH application, the original CT.GOV registration, and the original IRB documentation all suggest a smaller sample size (n=400), with only one primary effect modifier (Genotype Pattern).

The two joint primary analyses were informed by the literature, including our own previous research. The randomization was not unblinded and no analyses were conducted, until the study and all data cleanup were completed.

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eAppendix 2. Additional details on genotype assessment

The UK Biobank Axiom® Array was used for genome-wide genotyping in all participants. DNA samples with a genome-wide genotyping success rate of <95%, duplicate discordance or sex mismatch, genetic ancestry outliers (as determined by cluster analysis performed via principal-component analysis), SNPs with a genotyping success rate of <95%, monomorphic SNPs, SNPs with minor-allele frequency (MAF) <1%, and SNPs that mapped to several genomic locations were removed from the analyses. A total of 538959 UK Biobank SNPs were used for genotype imputation.

Imputation was performed on the Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html) using the reference panel released by the Haplotype Reference Consortium (http://www.haplotype-reference-consortium.org/). The variant rs1799883 was well imputed, with an imputation quality score (r^2) of 0.991.

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eAppendix 3. Additional rationale for SNPs selected for multi-locus genotype patterns at the time of grant application: Written in 2010

Although many specific gene variations have been associated with obesity and obesity related phenotypes,[1-5] only a small number of variations have been reported to have an effect on short-term weight loss in hypocaloric dietary intervention studies.[6-9] We are aware of only one study (10 weeks) that compared low carbohydrate and low fat diets and observed a genotype-diet interaction effect on weight loss.[10] Although gene variations that are associated with obesity should be relevant to weight loss, the translation into actionable information for more successful weight management is challenging.[11-13] We specifically focused on functional gene variations that had evidence of interactions with either dietary carbohydrate or fat relative to weight loss, and used the biological effect[12] of each allele to develop multi-locus genotype patterns that grouped all individuals by likelihood of being more carbohydrate sensitive, more fat sensitive, or a mixture of both (i.e., neither low carb or low fat). These genotype patterns were developed prior to the start of the study,[14] and the primary objective of the study was to explicitly assess the ability of the predetermined genetic patterns to predict improved weight loss relative to macronutrient content of the diet.

Lowering carbohydrates achieved better weight loss in subjects with the LCG pattern. This is consistent with evidence on biological effects attributable to allele G (12Ala) at the PPARG locus and allele G (27Glu) at the ADRB2 locus, that together constitute the LCG pattern. PPARγ protein regulates adipocyte formation and function, and the PPARG-12Ala genetic variant reduces DNA binding and activation of target genes.[15] Although not all studies agree on effects of PPARG variants, in general most studies report a strong diet-genotype interaction relative to body composition, with individuals carrying the 12Ala variant, i.e. allele G, being less sensitive to fat levels[16-18] and more likely than those with genotype C/C (12Pro/Pro) to be obese if their habitual carbohydrate intake exceeds 49% of energy.[19] In addition, women with the 12Ala variant regained more weight after a six month hypocaloric diet and had greater carbohydrate oxidation and less fat oxidation than those without the variant.[20] The LCG findings in the current study are also consistent with reports for individuals carrying ADRB2 allele G. The β-adrenergic receptors are involved in adipocyte lipid mobilization in response to catecholamines, and the ADRB2-27Gln/Glu polymorphism has been associated with obesity and altered adipocyte β-adrenergic receptor function.[21-23] In a cross-sectional study, women carrying the ADRB2 allele G (27Glu) who consumed above the median of 49% calories from carbohydrates had an increased risk for obesity and increased insulin levels compared to women who did not carry the genetic variant.[24]

The improved weight loss observed by lowering fat in subjects who were classified as an LFG pattern is consistent with previously reported biological effects attributable to carriage of allele A (54Thr) at the FABP2 locus and genotype C/C (Pro12Pro) at the PPARG locus, that together constitute the LFG pattern. The FABP2 allele A codes for a variant in the amino acid sequence (54Thr) of intestinal fatty acid binding protein 2 that is prominent in enterocytes. The variant has a two-fold greater binding affinity for long-chain fatty acids[25] and enhanced fat absorption and/or processing of dietary fatty acids by the intestine.[26] Multiple studies have shown that individuals with the FABP2-54Thr polymorphism respond differently to

Table 1. Multilocus genotype patterns

	Pattern	FABP2 Genotype rs 1799883 G>A[1] (Ala54Thr[2])	PPARG Genotype rs 1801282 C>G (Pro12Ala)	ADRB2 Genotype rs 1042714 C>G (Gln27Glu)	Frequency[3]
LFG	1	G**A**	**CC**	CC	0.140
	2	G**A**	**CC**	CG	0.137
	3	G**A**	**CC**	GG	0.040
	4	**A**A	**CC**	CC	0.037
	5	**A**A	**CC**	CG	0.027
LCG	6	GA	C**G**	C**G**	0.060
	7	GG	C**G**	C**G**	0.050
	8	GG	C**G**	G**G**	0.013
	9	AA	C**G**	C**G**	0.013
	10	GA	C**G**	G**G**	0.010
	11	GG	*CC*	C**G**	0.190
	12	GG	C**G**	CC	0.043
	13	*GA*	C**G**	CC	0.027
	14	GG	*CC*	G**G**	0.027
NG	15	GG	CC	CC	0.167

[1] Nucleotide transition at the indicated single-nucleotide polymorphism; where G>A indicates that the guanine nucleotide is more common than the adenine nucleotide
[2] The amino acid substitution that results from the nucleotide at the specified genomic location; where Ala54Thr indicates an alanine amino acid at position 54 in the peptide results from a G nucleotide and a threonine amino acid substitutes for the alanine when an the A nucleotide is present.
[3] Frequency calculated from a U.S. population sample (N=300) of unknown ethnicity

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dietary fat compared to those without the polymorphism, including higher levels of non-esterified fatty acids after a high-fat meal,[27] increased postprandial levels of triglycerides,[28] glucose, and lipogenesis.[29] The PPARG allele G codes for an altered protein (12Ala) variant that has decreased binding affinity of the PPAR with its response element and decreased PPARγ activity.[15] In addition, in adipocyte cell models, the 12Pro protein had increased adipocyte differentiation compared to the 12Ala variant.[30] Individuals with the PPARG genotype C/C (12Pro/Pro), a component of the LFG, display increased adiposity and higher BMI and waist circumference in the presence of high total fat intake and may be more resistant to weight loss compared to those carrying the 12Ala variant.[16,17,31]

Some gene variants associated with obesity, including those evaluated in this study, have been associated with disruption of pathways involved in energy intake and satiety[32] Examples include higher food intake in individuals carrying the FABP2-54Thr vs. FABP2-54Ala form of the protein,[33] compensatory eating behaviors in individuals with variants of PPARG and ADRB3 genes,[34] and higher satiety in individuals with the PPARG (12Pro/*) and ADRB2 (27Glu/*) variants compared to those in the PPARG (Pro12Pro) and ADRB2 (Gln27Gln) group.[35] These findings are consistent with the observed trend toward lower reported daily Kcal intake among those assigned to a diet matched to their genotype pattern in the current study.

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eAppendix 4. Statistical model

$$
\begin{aligned}
weight_{ij} = \propto_0 + \gamma_i + \beta_1\, LC\ diet_i + \beta_2\, LC\ geno_i + \beta_3 3m\ visit_{ij} + \beta_4 6m\ visit_{ij} \\
+ \beta_5 12m\ visit_{ij} + \beta_6\, LC\ diet_i \times LC\ geno_i + \beta_7 LC\ diet_i \times 3m\ visit_{ij} \\
+ \beta_8 LC\ diet_i \times 6m\ visit_{ij} + \beta_9 LC\ diet_i \times 12m\ visit_{ij} + \beta_{10} LC\ geno_i \\
\times 3m\ visit_{ij} \\
+ \beta_{11} LC\ geno_i \times 6m\ visit_{ij} + \beta_{12} LC\ geno_i \times 12m\ visit_{ij} + \beta_{13} LC\ diet_i \\
\times LC\ geno_i \times 3m\ visit_{ij} \\
+ \beta_{14} LC\ diet_i \times LC\ geno_i \times 6m\ visit_{ij} + \beta_{15} LC\ diet_i \times LC\ geno_i \\
\times 12m\ visit_{ij} + \epsilon_{_ij}
\end{aligned}
$$

In the above, the $\propto$ and β terms are fixed effects, γ_i is a random effect for subject i, and $\epsilon_{_ij}$ is an error term for subject i at timepoint j (j=0 is baseline, j=1 is 3 months, j=2 is 6 months, and j=3 is 12 months). We are most interested in the fixed effect β_{15}, as if it is non-zero, the model gives evidence that there is a statistically significant interaction between diet and genotype on 12 month weight change. The above model is also used for inference on the possible diet-insulin interaction with the same model structure and the substitution of genotype with continuous baseline insulin-30.

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eTable 1. Anthropometric and Metabolic Variables, All Time Points Mean (SD) and Estimates (95% Confidence Intervals) for Difference by Diet

	Healthy Low Fat (HLF)		Healthy Low Carb (HLC)		HLF-HLC diff (95% CI)[a]
Weight (kg)					
Baseline	N=305	97.5 (14.7)	N=304	96.3 (15.7)	1.3 (-1.1, 3.6)
3 Months	N=270	91.7 (14.1)	N=263	89.4 (15.1)	2.4 (0, 4.8)
6 Months	N=228	90.0 (13.9)	N=239	87.2 (14.7)	2.6 (0.2, 5)
12 Months	N=216	91.0 (14.9)	N=220	88.7 (15.7)	2 (-0.5, 4.4)
BMI (kg/m^2)					
Baseline	N=305	33.4 (3.4)	N=304	33.3 (3.4)	0.1 (-0.5, 0.7)
3 Months	N=270	31.6 (3.6)	N=263	31.0 (3.6)	0.6 (0, 1.2)
6 Months	N=228	31.2 (3.8)	N=239	30.4 (3.6)	0.7 (0.1, 1.3)
12 Months	N=216	31.5 (4.0)	N=220	30.8 (3.9)	0.4 (-0.2, 1)
Fat (%)					
Baseline	N=228	36.3 (6.9)	N=238	36.5 (6.6)	-0.3 (-1.6, 1)
6 Months	N=182	33.9 (7.7)	N=194	33.6 (7.3)	0.5 (-0.8, 1.7)
12 Months	N=185	33.8 (7.8)	N=196	33.8 (7.0)	-0.1 (-1.4, 1.2)
Waist circumference (cm)					
Baseline	N=302	107.2 (10.9)	N=302	106.7 (11.4)	0.6 (-1.1, 2.3)
3 Months	N=269	103.5 (10.3)	N=261	101.9 (10.7)	1.5 (-0.2, 3.3)
6 Months	N=228	102.7 (9.8)	N=238	100.9 (10.4)	1.7 (-0.1, 3.5)
12 Months	N=216	103.1 (11.0)	N=220	101.2 (10.9)	1.3 (-0.6, 3.1)
LDL (mmol/L)					
Baseline	N=305	2.89 (0.79)	N=303	2.94 (0.68)	-0.06 (-0.18, 0.06)
3 Months	N=269	2.79 (0.83)	N=264	3.24 (0.76)	-0.43 (-0.55, -.0.31)
6 Months	N=225	2.77 (0.76)	N=239	3.09 (0.74)	-0.28 (-0.41, -0.15)
12 Months	N=216	2.81 (0.76)	N=219	3.10 (0.69)	-0.21 (-0.33, -0.08)
HDL (mmol/L)					
Baseline	N=305	1.28 (0.23)	N=304	1.29 (0.24)	-0.01 (-0.05,0.03)
3 Months	N=269	1.25 (0.24)	N=264	1.32 (0.22)	-0.07 (-0.11, -0.04)
6 Months	N=225	1.23 (0.23)	N=239	1.33 (0.22)	-0.09 (-0.12, -0.05)
12 Months	N=216	1.28 (0.25)	N=219	1.37 (0.24)	-0.07 (-0.11, -0.03)
Triglycerides (mmol/L)					
Baseline	N=305	1.45 (0.80)	N=304	1.45 (1.03)	0.01 (-0.11, 0.13)
3 Months	N=269	1.42 (0.79)	N=264	1.12 (0.54)	0.3 (0.18, 0.43)
6 Months	N=225	1.29 (0.64)	N=239	1.09 (0.57)	0.2 (0.07, 0.33)
12 Months	N=216	1.34 (0.73)	N=219	1.14 (0.66)	0.21 (0.08, 0.34)

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	Healthy Low Fat (HLF)		Healthy Low Carb (HLC)		HLF-HLC diff (95% CI)[a]
eTable 1 (continued)					
Systolic BP (mmHg)					
Baseline	N=303	122.9 (12.5)	N=303	122.9 (12.4)	-0.1 (-2, 1.8)
3 Months	N=270	119.7 (12.0)	N=264	117.4 (11.2)	2.2 (0.3, 4.2)
6 Months	N=228	120.0 (11.7)	N=239	117.8 (11.1)	1.9 (-0.1, 3.9)
12 Months	N=216	120.0 (10.8)	N=220	119.1 (11.8)	0.5 (-1.6, 2.5)
Diastolic BP (mmHg)					
Baseline	N=303	81.0 (7.3)	N=303	81.2 (7.8)	-0.2 (-1.4, 0.9)
3 Months	N=270	78.6 (7.3)	N=264	77.1 (7.0)	1.6 (0.4, 2.8)
6 Months	N=228	78.9 (7.6)	N=239	77.9 (7.1)	0.9 (-0.4, 2.1)
12 Months	N=216	79.2 (6.7)	N=220	78.3 (7.3)	0.5 (-0.8, 1.7)
Fasting insulin (uu/mL)					
Baseline	N=305	15.9 (13.5)	N=304	15.5 (8.0)	0.4 (-0.9, 1.7)
3 Months	N=270	15.2 (6.9)	N=264	14.7 (7.6)	0.4 (-1, 1.9)
6 Months	N=225	13.1 (8.9)	N=239	11.9 (5.5)	1.0 (-0.5, 2.5)
12 Months	N=216	13.2 (6.3)	N=219	12.6 (5.9)	0.1 (-1.4, 1.6)
Insulin-30 (uu/mL)[b]					
Baseline	N=302	95.1 (67.5)	N=304	91.8 (61.7)	3.4 (-6.2, 13)
6 Months	N=222	71.1 (52.3)	N=239	69.2 (47.9)	-0.2 (-10.5, 10)
12 Months	N=212	78.4 (54.2)	N=215	74.0 (49.7)	-0.5 (-10.9, 10)
Fasting glucose (mg/dL)					
Baseline	N=305	98.6 (8.6)	N=304	98.5 (9.7)	0.2 (-1.3, 1.7)
3 Months	N=270	97.5 (9.1)	N=263	98.5 (9.4)	-0.9 (-2.4, 0.7)
6 Months	N=225	95.3 (9.6)	N=239	96.2 (9.3)	-0.8 (-2.4, 0.9)
12 Months	N=216	94.9 (9.6)	N=219	96.2 (10.3)	-1.4 (-3.1, 0.3)
Metabolic syndrome[c] (%)					
Baseline	N=305	106 (34.8%)	N=304	100 (32.9%)	
3 Months	N=270	86 (31.9%)	N=264	60 (22.7%)	
6 Months	N=228	54 (23.7%)	N=239	48 (20.1%)	
12 Months	N=216	52 (24.1%)	N=220	47 (21.4%)	
Respiratory Exchange Ratio					
Baseline	N=264	0.861 (0.065)	N=264	0.862 (0.058)	-0.001 (-0.011,0.009)
6 Months	N=195	0.860 (0.063)	N=210	0.827 (0.045)	0.033 (0.022, 0.045)
12 Months	N=187	0.853 (0.063)	N=193	0.834 (0.058)	0.019 (0.007, 0.031)

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	Healthy Low Fat (HLF)		Healthy Low Carb (HLC)		HLF-HLC diff (95% CI)[a]
eTable 1 (continued)					
Resting Energy Expenditure					
Baseline	N=264	1650.5 (282.5)	N=264	1628.7 (293.4)	21.6 (-25.7, 68.8)
6 Months	N=195	1563.2 (251.6)	N=210	1541.2 (283.3)	22.7 (-28.1, 73.4)
12 Months	N=187	1576.9 (245.1)	N=193	1540.3 (262.8)	32.1 (-19.5, 83.6)
Total Energy Expenditure					
Baseline	N=282	32.6 (1.7)	N=271	32.5 (2.2)	0.1 (-0.3, 0.4)
3 Months	N=246	33.2 (2.3)	N=247	32.8 (2.3)	0.4 (0, 0.8)
6 Months	N=198	33.1 (2.2)	N=195	33.0 (2.4)	0.1 (-0.3, 0.6)
12 Months	N=198	33.1 (2.5)	N=200	33.1 (2.6)	0 (-0.4, 0.4)

HLF = Healthy Low-Fat; HLC = Healthy Low-Carb

[a]Estimate (95% confidence interval) for HLF minus HLC difference from linear mixed model

[b] INS-30 is the blood concentration of insulin at the 30 minute time point of an Oral Glucose Tolerance Test

[c]P-value of 0.30 from 3 degree of freedom test for no diet by time interaction in generalized linear mixed effects model

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eTable 2A. Baseline Demographics by Diet-Genotype Group; n (%), or mean (SD)

	Healthy Low Fat Diet			Healthy Low Carb Diet		
	Low Carb Genotype	**Low Fat Genotype**	**Neither Genotype**	**Low Carb Genotype**	**Low Fat Genotype**	**Neither Genotype**
	n=83	n=130	n=70	n=97	n=114	n=76
Gender						
Women	40 (48.2%)	75 (57.7%)	42 (60.0%)	57 (58.8%)	69 (60.5%)	40 (52.6%)
Men	43 (51.8%)	55 (42.3%)	28 (40.0%)	40 (41.2%)	45 (39.5%)	36 (47.4%)
Age	40.2 (7.0)	38.3 (6.7)	39.1 (6.6)	41.4 (6.2)	39.4 (7.0)	39.7 (6.7)
Education, highest achieved (years)						
Some grade school (≤ 8)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	2 (1.8%)	0 (0.0%)
Some high school (9-11)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
High school graduate (12)	0 (0.0%)	2 (1.5%)	2 (2.9%)	5 (5.2%)	2 (1.8%)	3 (3.9%)
Some college (13-15)	11 (13.3%)	28 (21.5%)	16 (22.9%)	22 (22.7%)	25 (21.9%)	17 (22.4%)
College graduate (16)	36 (43.4%)	43 (33.1%)	21 (30.0%)	32 (33.0%)	49 (43.0%)	21 (27.6%)
Some postgraduate school (≥ 17)	9 (10.8%)	11 (8.5%)	3 (4.3%)	3 (3.1%)	4 (3.5%)	4 (5.3%)
Post-graduate degree (18+)	26 (31.3%)	44 (33.8%)	28 (40.0%)	34 (35.1%)	31 (27.2%)	30 (39.5%)
Missing	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Race/ethnicity						
White	62 (74.7%)	72 (55.4%)	32 (45.7%)	71 (73.2%)	64 (56.1%)	37 (48.7%)
Hispanic	13 (15.7%)	27 (20.8%)	18 (25.7%)	18 (18.6%)	26 (22.8%)	15 (19.7%)
Asian	4 (4.8%)	15 (11.5%)	10 (14.3%)	6 (6.2%)	12 (10.5%)	10 (13.2%)
African American	0 (0.0%)	5 (3.8%)	4 (5.7%)	1 (1.0%)	6 (5.3%)	5 (6.6%)
AI/AN/PI	1 (1.2%)	1 (0.8%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	3 (3.6%)	10 (7.7%)	5 (7.1%)	1 (1.0%)	6 (5.3%)	9 (11.8%)
Weight (kg)	98.2 (13.7)	98.0 (16.0)	96.5 (13.6)	96.0 (14.7)	95.9 (16.6)	97.5 (16.3)
BMI (kg/m^2)	33.0 (3.0)	33.7 (3.3)	33.9 (3.3)	33.6 (3.4)	33.1 (3.4)	33.3 (3.4)
Body fat (%)	34.7 (6.8)	37.5 (7.1)	37.0 (6.5)	36.9 (6.8)	36.8 (6.7)	35.1 (6.1)
Missing	19 (22.9%)	37 (28.5%)	16 (22.9%)	23 (23.7%)	25 (21.9%)	16 (21.1%)

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	Healthy Low Fat Diet			Healthy Low Carb Diet		
	Low Carb Genotype	**Low Fat Genotype**	**Neither Genotype**	**Low Carb Genotype**	**Low Fat Genotype**	**Neither Genotype**
eTable 2a (continued)						
Waist circumference (cm)	106.9 (10.7)	107.3 (10.6)	108.0 (12.0)	106.8 (10.8)	106.4 (11.5)	107.2 (12.6)
Missing	2 (2.4%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	2 (2.6%)
Blood Lipids (mmol/L)						
LDL-C	2.93 (0.83)	2.86 (0.76)	2.90 (0.80)	2.99 (0.67)	2.92 (0.63)	2.93 (0.73)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.3%)
HDL-C	1.29 (0.24)	1.26 (0.23)	1.28 (0.22)	1.28 (0.22)	1.29 (0.23)	1.29 (0.27)
Triglycerides	1.59 (0.83)	1.37 (0.70)	1.44 (0.90)	1.41 (0.64)	1.32 (0.61)	1.63 (1.60)
Blood pressure (mmHg)						
Systolic	124.4 (11.3)	121.1 (12.2)	124.5 (14.1)	123.0 (13.3)	122.0 (12.1)	124.2 (12.6)
Missing	1 (1.2%)	1 (0.8%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
Diastolic	81.5 (6.9)	80.5 (6.9)	82.4 (9.0)	81.4 (8.1)	80.6 (7.4)	82.0 (8.9)
Missing	1 (1.2%)	1 (0.8%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
Fasting glucose (mg/dL)	98.0 (7.6)	99.2 (9.2)	97.0 (8.9)	98.5 (9.3)	98.7 (10.4)	97.7 (9.9)
Fasting insulin (uU/mL)	15.0 (6.7)	17.0 (18.1)	15.8 (10.7)	14.9 (6.5)	15.0 (9.4)	16.8 (7.8)
Insulin-30 (uU/mL)[a]	96.3 (53.4)	95.3 (60.7)	99.5 (96.1)	82.8 (48.1)	89.2 (63.5)	103.8 (60.2)
Missing	0 (0%)	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Metabolic Syndrome[b]	26 (31.3%)	47 (36.2%)	25 (35.7%)	36 (37.1%)	33 (28.9%)	24 (31.6%)
Respiratory Exchange Ratio	0.87 (0.08)	0.86 (0.06)	0.86 (0.06)	0.85 (0.06)	0.87 (0.06)	0.86 (0.06)
Missing	12 (14.5%)	20 (15.4%)	8 (11.4%)	14 (14.4%)	14 (12.3%)	12 (15.8%)
Resting Energy Expenditure (kcal)	1685.0 (267.2)	1655.4 (303.0)	1608.1 (274.5)	1620.1 (248.5)	1625.2 (331.2)	1654.0 (311.0)
Missing	12 (14.5%)	20 (15.4%)	8 (11.4%)	14 (14.4%)	14 (12.3%)	12 (15.8%)
Energy Expenditure (kcal/kg/day)	32.7 (1.4)	32.7 (1.9)	32.3 (1.8)	32.7 (2.1)	32.1 (2.4)	32.9 (2.0)
Missing	6 (7.2%)	10 (7.7%)	5 (7.1%)	11 (11.3%)	10 (8.8%)	6 (7.9%)

AI/AN/PI = AI=American Indian, AN=Alaska Native, PI=Pacific Islander ; BMI = Body Mass Index; LDL-C = Low Density Lipoprotein Cholesterol; HDL-C = High Density Lipoprotein Cholesterol

[a] INS-30 is the blood concentration of insulin at the 30 minute time point of an Oral Glucose Tolerance Test

[b] Metabolic syndrome as defined by ATP III guidelines[40]

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eTable 2B. Baseline Demographics by Ins-30 Diet Group; n (%) or mean (SD). Insulin-30 Range Given for Each Tertile

	Healthy Low Fat Diet			Healthy Low Carb Diet		
Tertiles	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**
Range (uU/mL)	7.3-60.6	60.7-103.1	103.4-562.5	7.3-60.6	60.7-103.1	103.4-562.5
	n=96	n=105	n=101	n=106	n=97	n=101
Gender						
Women	58 (60.4%)	57 (54.3%)	50 (49.5%)	70 (66.0%)	59 (60.8%)	50 (49.5%)
Men	38 (39.6%)	48 (45.7%)	51 (50.5%)	36 (34.0%)	38 (39.2%)	51 (50.5%)
Age	39.8 (6.9)	39.3 (6.5)	39.0 (7.0)	41.5 (6.1)	39.7 (7.0)	39.4 (7.0)
Education, highest achieved (years)						
Some grade school (≤ 8)	0 (0.0%)	1 (1.0%)	0 (0.0%)	2 (1.9%)	1 (1.0%)	0 (0.0%)
Some high school (9-11)	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
High school graduate (12)	3 (3.1%)	2 (1.9%)	0 (0.0%)	5 (4.7%)	3 (3.1%)	3 (3.0%)
Some college (13-15)	21 (21.9%)	21 (20.0%)	20 (19.8%)	20 (18.9%)	23 (23.7%)	24 (23.8%)
College graduate (16)	29 (30.2%)	39 (37.1%)	33 (32.7%)	34 (32.1%)	36 (37.1%)	36 (35.6%)
Some postgraduate school (≥ 17)	7 (7.3%)	7 (6.7%)	11 (10.9%)	3 (2.8%)	6 (6.2%)	3 (3.0%)
Post-graduate degree (18+)	36 (37.5%)	35 (33.3%)	35 (34.7%)	41 (38.7%)	28 (28.9%)	34 (33.7%)
Missing	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Race/ethnicity						
White	62 (64.6%)	62 (59.0%)	50 (49.5%)	69 (65.1%)	61 (62.9%)	52 (51.5%)
Hispanic	21 (21.9%)	19 (18.1%)	26 (25.7%)	22 (20.8%)	15 (15.5%)	24 (23.8%)
Asian	4 (4.2%)	11 (10.5%)	15 (14.9%)	7 (6.6%)	10 (10.3%)	13 (12.9%)
African American	6 (6.2%)	2 (1.9%)	2 (2.0%)	4 (3.8%)	5 (5.2%)	4 (4.0%)
AI/AN/PI	0 (0.0%)	1 (1.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	3 (3.1%)	10 (9.5%)	6 (5.9%)	4 (3.8%)	6 (6.2%)	8 (7.9%)
Weight (kg)	94.9 (13.1)	96.0 (14.2)	101.5 (16.0)	92.7 (13.1)	96.9 (16.4)	99.4 (16.8)
BMI (kg/m^2)	32.7 (3.4)	33.2 (3.3)	34.2 (3.2)	32.5 (3.4)	33.8 (3.4)	33.7 (3.3)
Body fat (%)	36.1 (7.3)	36.2 (6.8)	36.7 (6.7)	36.8 (7.0)	37.3 (6.3)	35.3 (6.3)
Missing	20 (20.8%)	25 (23.8%)	31 (30.7%)	22 (20.8%)	17 (17.5%)	27 (26.7%)
eTable 2b (continued)	104.3 (10.3)	106.5 (10.1)	110.9 (11.5)	103.3 (9.7)	107.0 (11.1)	109.9 (12.4)

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	Healthy Low Fat Diet			Healthy Low Carb Diet		
Tertiles	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**
Range (uU/mL)	7.3-60.6	60.7-103.1	103.4-562.5	7.3-60.6	60.7-103.1	103.4-562.5
Waist circumference(cm)						
Missing	0 (0%)	1 (1.0%)	2 (2.0%)	1 (0.9%)	1 (1.0%)	0 (0%)
Blood Lipids (mmol/L)						
LDL-C	2.73 (0.74)	2.96 (0.82)	2.96 (0.80)	3.11 (0.61)	2.86 (0.65)	2.85 (0.73)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.99%)
HDL-C	1.32 (0.23)	1.28 (0.22)	1.24 (0.23)	1.36 (0.23)	1.29 (0.24)	1.20 (0.22)
Triglycerides	101.8 (58.9)	130.3 (66.9)	152.8 (78.6)	108.1 (47.0)	126.4 (60.9)	150.4 (136.0)
Blood pressure (mmHg)						
Systolic	121.6 (12.6)	124.4 (13.6)	122.6 (11.4)	120.6 (10.9)	124.6 (14.7)	123.6 (11.1)
Missing	0 (0%)	2 (1.9%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Diastolic	80.0 (6.8)	81.9 (8.2)	81.1 (6.8)	79.4 (6.3)	82.3 (8.8)	82.0 (7.8)
Missing	0 (0%)	2 (1.9%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
Fasting glucose (mmol/L)	97.2 (8.6)	99.4 (9.1)	99.3 (8.0)	97.6 (9.8)	98.2 (9.0)	99.6 (10.3)
Fasting insulin (uU/mL)	11.0 (4.5)	14.1 (5.8)	22.3 (20.7)	10.9 (4.7)	14.9 (5.3)	20.8 (9.6)
Insulin-30 (uU/mL)[a]	41.1 (13.0)	78.9 (12.0)	163.4 (74.9)	40.5 (12.8)	81.3 (11.8)	155.7 (64.8)
Metabolic Syndrome[b]	23 (24.0%)	36 (34.3%)	47 (46.5%)	21 (19.8%)	36 (37.1%)	43 (42.6%)
Respiratory Exchange Ratio	0.86 (0.06)	0.87 (0.07)	0.86 (0.06)	0.85 (0.06)	0.86 (0.06)	0.87 (0.05)
Missing	8 (8.3%)	14 (13.3%)	19 (18.8%)	16 (15.1%)	10 (10.3%)	14 (13.9%)
Resting Energy Expenditure (kcal)	1599.5 (261.5)	1668.5 (274.5)	1682.9 (311.8)	1545.9 (212.8)	1623.2 (296.5)	1719.8 (335.8)
Missing	8 (8.3%)	14 (13.3%)	19 (18.8%)	16 (15.1%)	10 (10.3%)	14 (13.9%)
Energy Expenditure (kcal/kg/day)	32.9 (1.4)	32.4 (1.9)	32.4 (1.9)	32.9 (2.3)	32.5 (2.2)	32.1 (2.0)
Missing	4 (4.2%)	10 (9.5%)	9 (8.9%)	9 (8.5%)	15 (15.5%)	9 (8.9%)

AI/AN/PI = AI=American Indian, AN=Alaska Native, PI=Pacific Islander ; BMI = Body Mass Index; LDL-C = Low Density Lipoprotein Cholesterol; HDL-C = High Density Lipoprotein Cholesterol

[a] INS-30 is the blood concentration of insulin at the 30 minute time point of an Oral Glucose Tolerance Test

[b] Metabolic syndrome as defined by ATP III guidelines[40]

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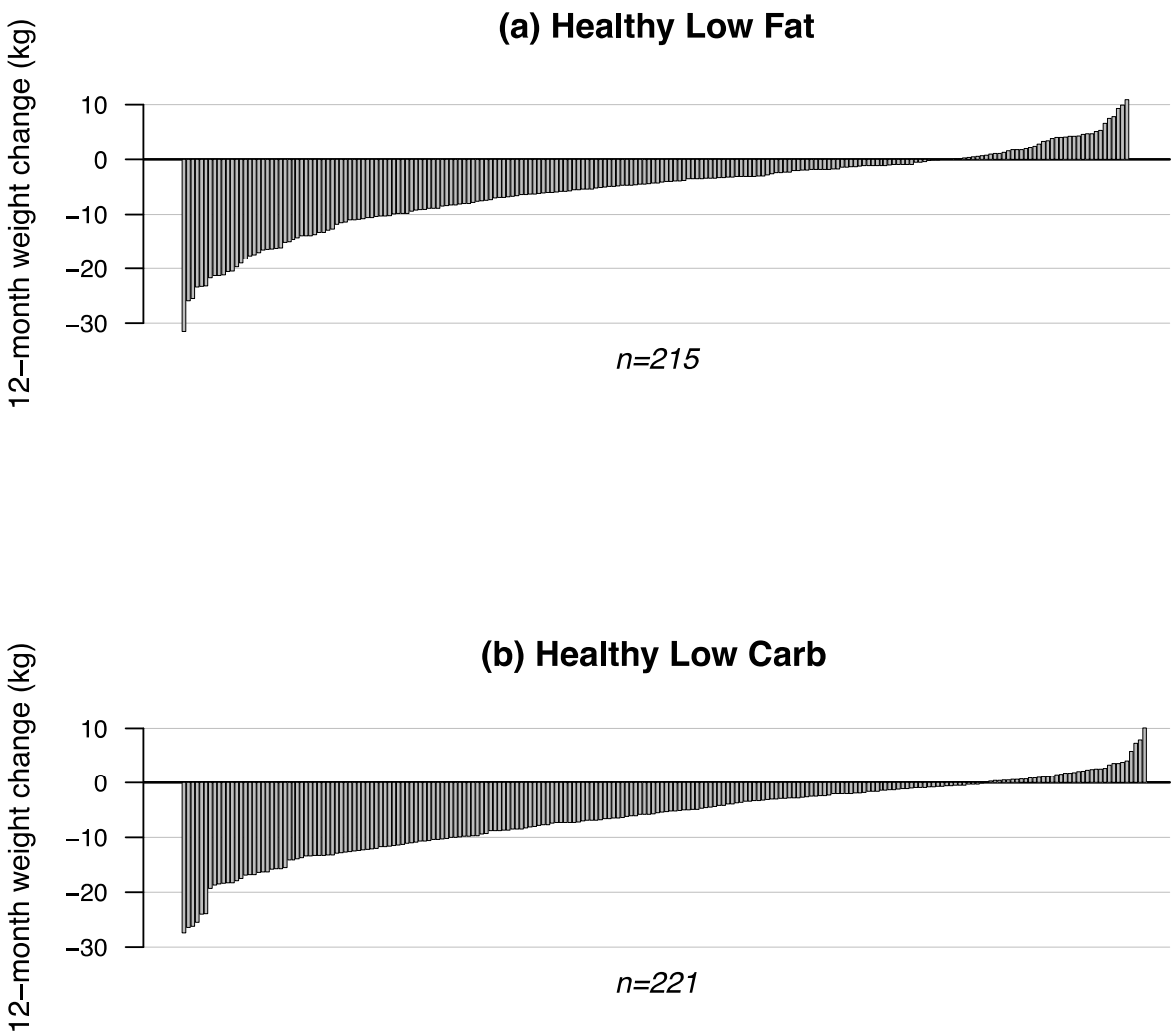
eFigure 1. Waterfall plot of weight loss by diet group



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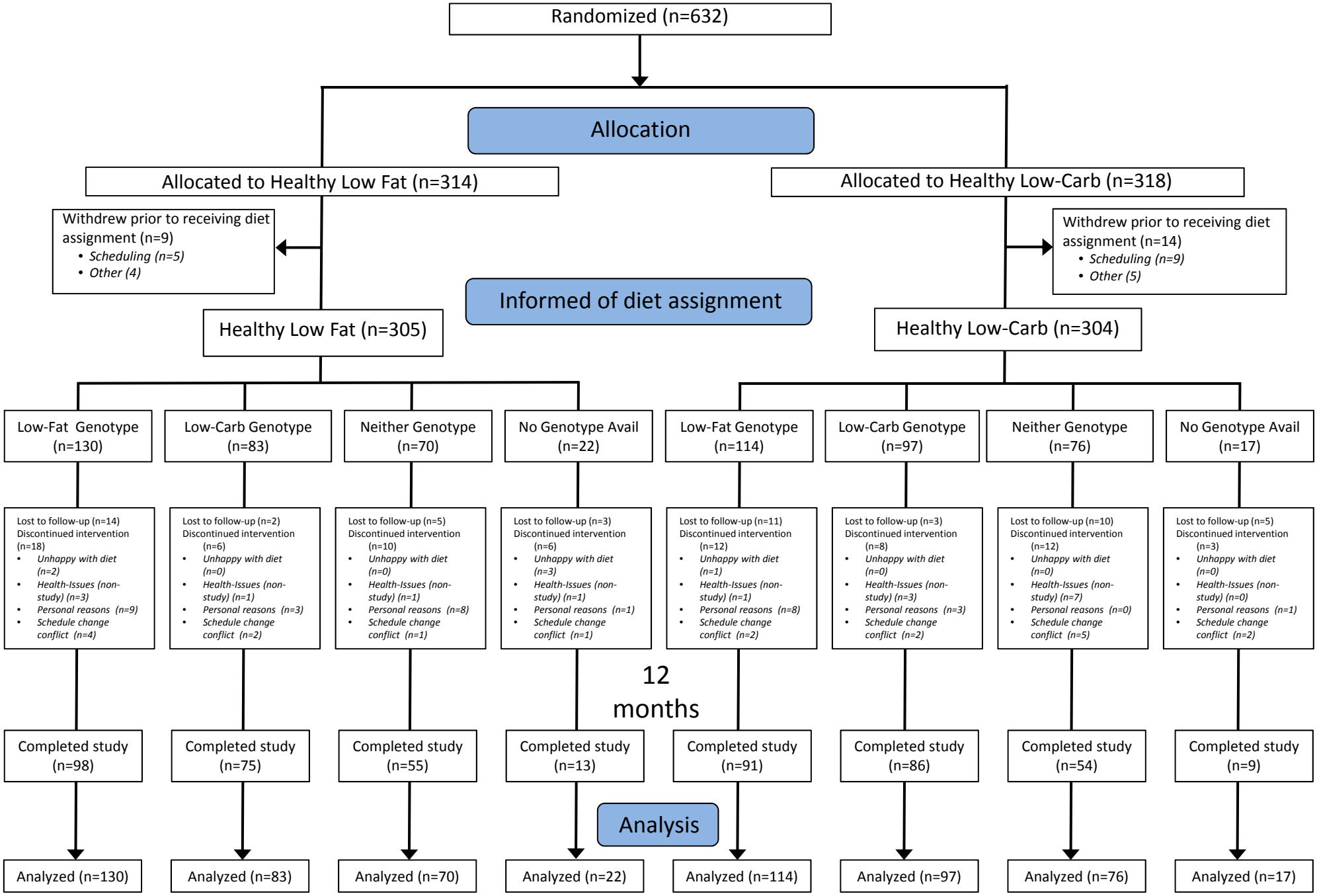
eFigure2a. Participant Flow by Genotype Pattern and Diet Group



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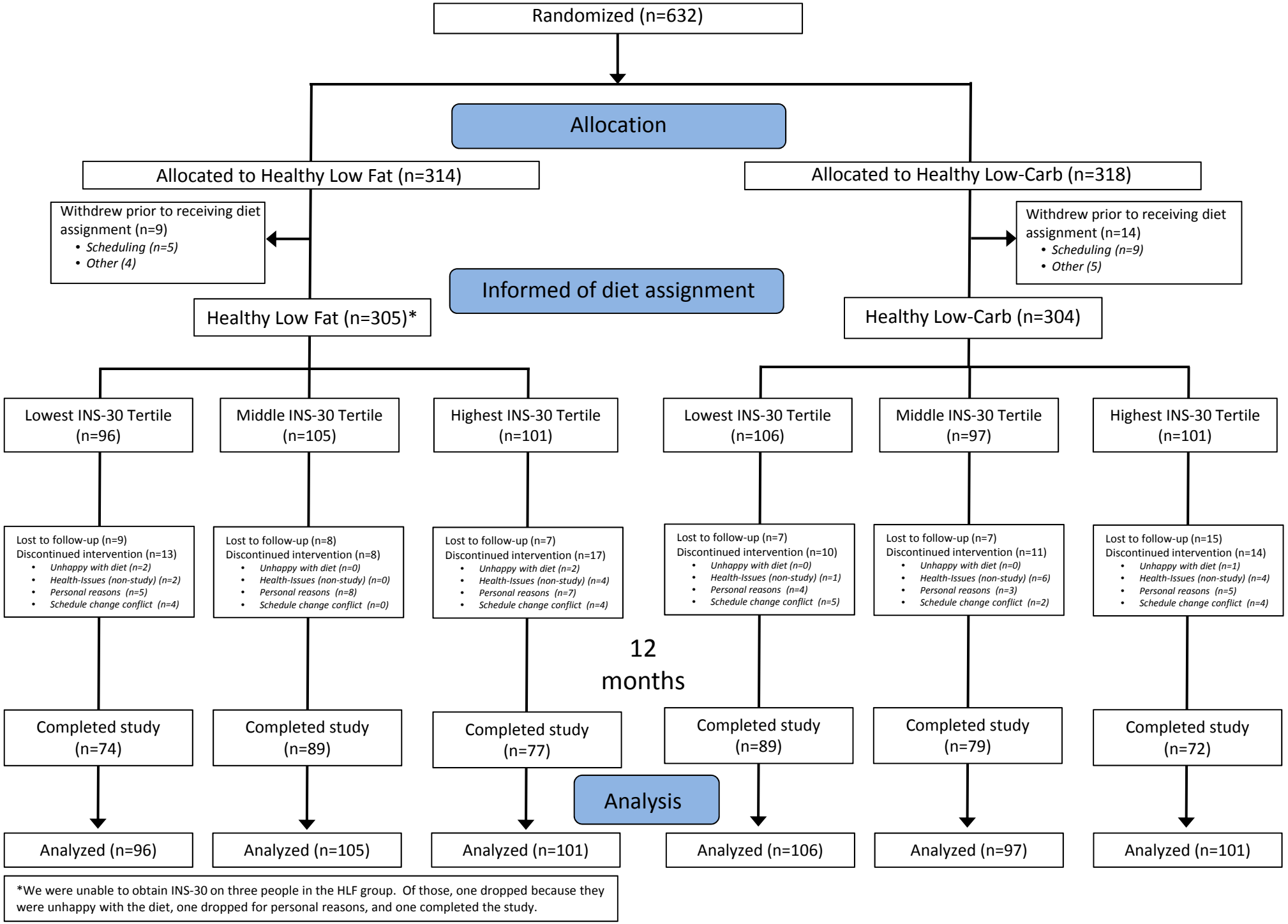
eFigure2b. Participant Flow by INS-30 Tertile and Diet Group



*We were unable to obtain INS-30 on three people in the HLF group. Of those, one dropped because they were unhappy with the diet, one dropped for personal reasons, and one completed the study.

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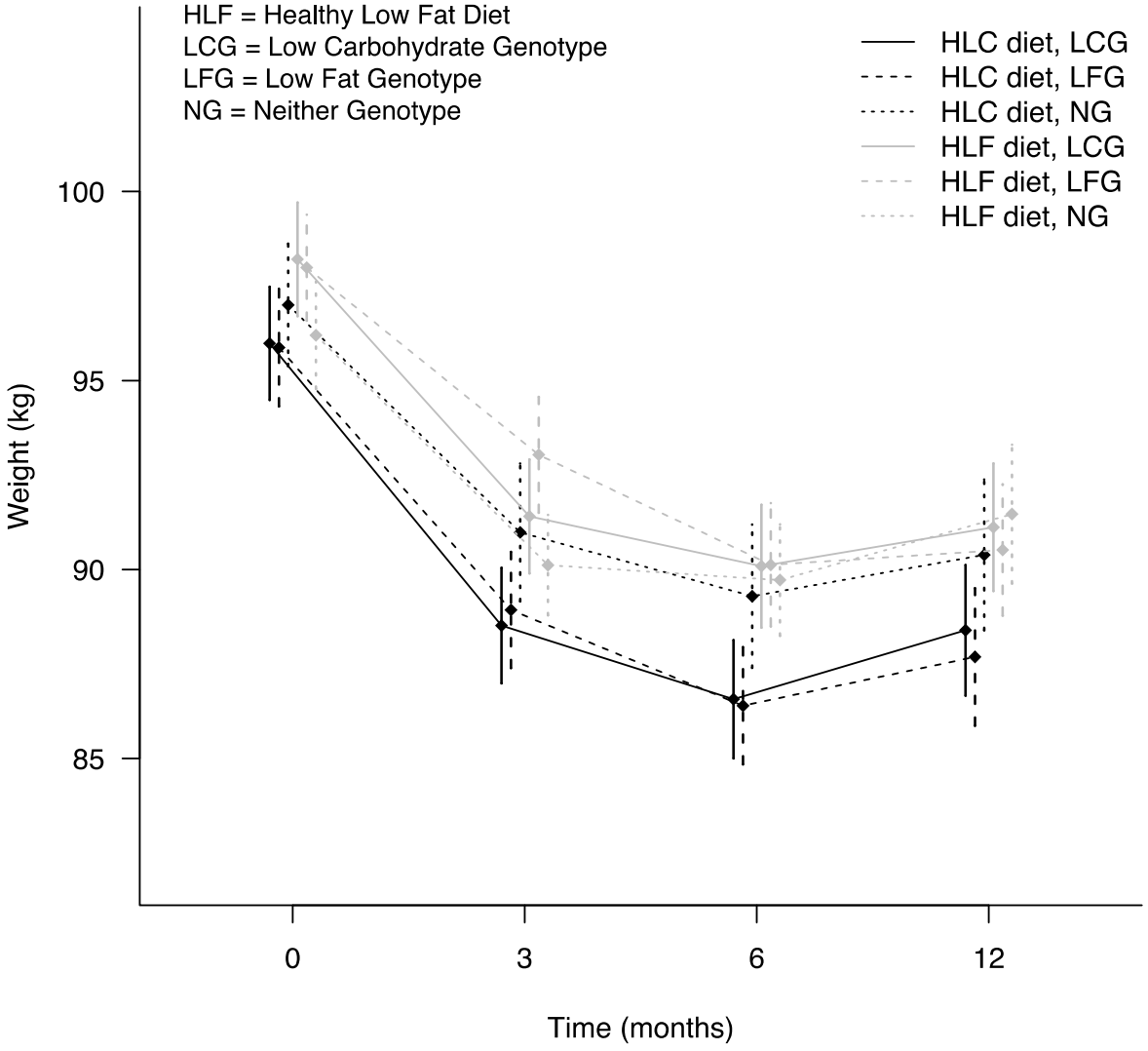
eFigure 3a. Weight trajectory over 12 months for 6 subgroups (mean, SE):
2 Diet Groups X 3 Genotype Patterns
HLC = Healthy Low Carbohydrate Diet
HLF = Healthy Low Fat Diet
LCG = Low Carbohydrate Genotype
LFG = Low Fat Genotype
NG = Neither Genotype



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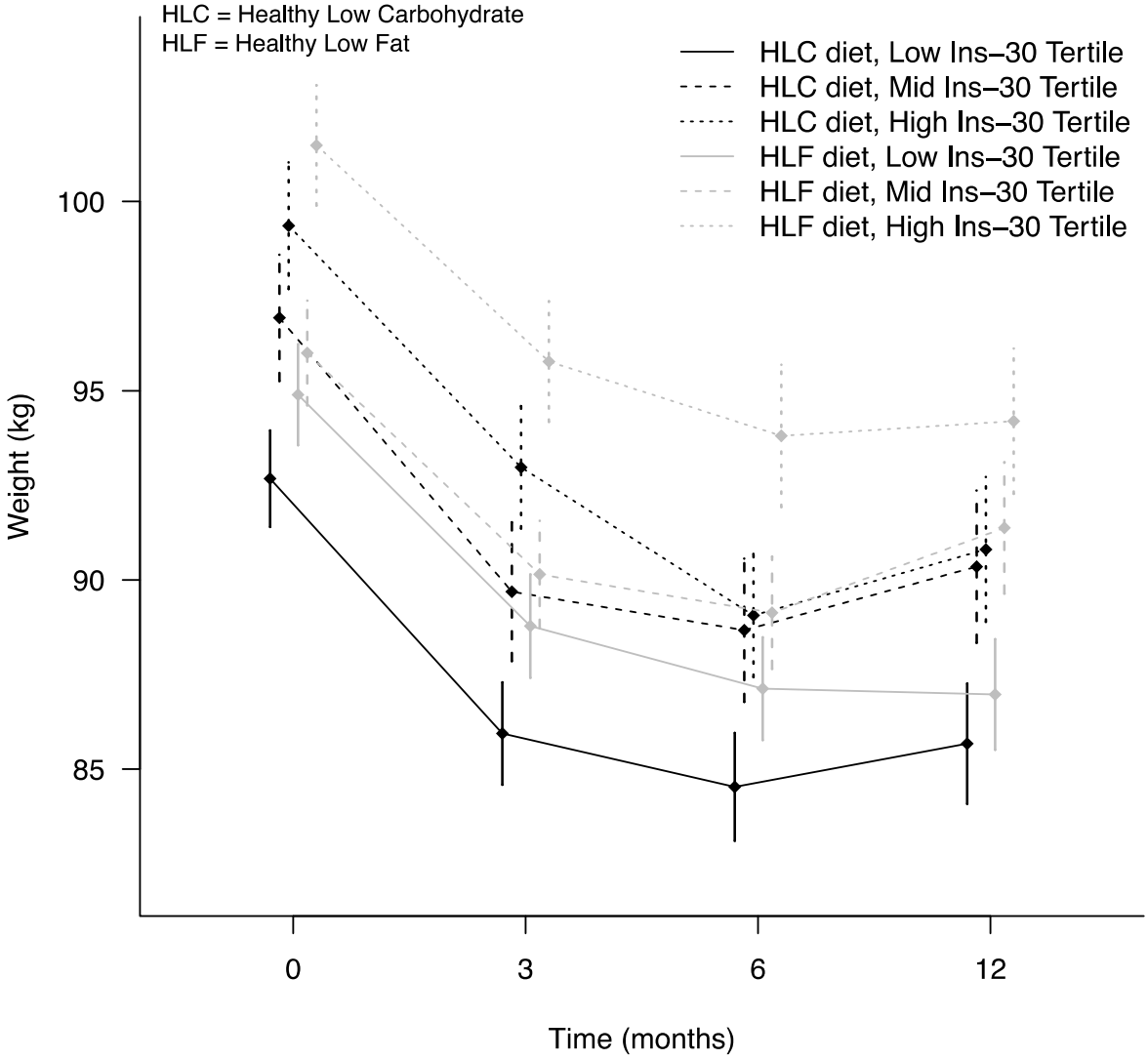
eFigure 3b. Weight trajectory over 12 months for 6 subgroups:
2 Diet Groups X 3 Tertiles of INS-30
INS-30 is the blood concentration of insulin at the 30 minute time point of an Oral Glucose Tolerance Test
HLC = Healthy Low Carbohydrate
HLF = Healthy Low Fat



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