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Growth Differentiation Factor 15 and Diet Quality Trajectory Interact to Determine Frailty Incidence among Middle-Aged Urban Adults

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A B S T R A C T

Background: Elevated plasma growth differentiation factor 15 (GDF15) and poor diet quality may be associated with increased frailty incidence, although their interactive associations have not been assessed in urban middle-aged adults.
Objectives: We aimed to examine GDF15 and its interactive association with diet quality in relation to frailty incidence among a sample of middle-aged urban adults.
Methods: The relationship between GDF15 and diet quality trajectories in relation to incident frailty was examined in a longitudinal study of participants in the Healthy Aging in Neighborhoods of Diversity across the Life Span (2004–2017). Serum GDF15 concentration and frailty incidence were primary exposure and outcome, respectively. Group-based trajectory models were used to assess diet quality trajectories (≤3 visits/participant, $N = 945$, $N' = 2247$ observations) using the Healthy Eating Index 2010 version (HEI-2010), Dietary Inflammatory Index, and mean adequacy ratio (MAR). Cox proportional hazards models were used, testing interactive associations of GDF15 and diet quality trajectories with frail/prefrail incidence ($N = 400$ frailty-free at first visit, $N' = 604$ observations, $n = 168$ incident frail/prefrail).
Results: Both elevated GDF15 and lower diet quality trajectories were associated with a lower probability of remaining nonfrail (≤13 y follow-up). Among females, the "high diet quality" HEI-2010 trajectory had a hazard ratio (HR) of 0.15 [95% confidence interval (CI): 0.04, 0.54; $P = 0.004$; fully adjusted model] when compared with the "low diet quality" trajectory group. Among males only, there was an antagonistic interaction between lower HEI-2010 trajectory and elevated GDF15. Specifically, the HR for GDF15-frailty in the higher diet quality trajectory group (high/medium combined), and among males, was 2.69 (95% CI: 1.06, 6.62; $P = 0.032$), whereas among the lower diet quality trajectory group, the HR was 0.94 (95% CI: 0.49, 1.80; $P = 0.86$). Elevated GDF15 was independently associated with frailty among African American adults.
Conclusions: Pending replication, we found an antagonistic interaction between GDF15 and HEI-2010 trajectory in relation to frailty incidence among males.

Keywords: GDF15, diet, frailty, aging, race, health disparities

Abbreviations: AMPM, Automated Multiple-Pass Method; BIC, Bayesian information criterion; CRP, C-reactive protein; CI, confidence interval; CV, coefficient of variation; DGA, Dietary Guidelines for Americans; DII, Dietary Inflammatory Index; EGFR, epidermal growth factor receptor; GBTM, group-based trajectory model; GDF15, growth differentiation factor 15; GDNF, glial cell-derived neurotrophic factor; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; HEI, Healthy Eating Index; HEI-2010, Healthy Eating Index 2010 version; HR, hazard ratio; ln, natural logarithm; MAR, mean adequacy ratio; MRV, medical research vehicle; NAR, nutrient adequacy ratio; PH, proportional hazards; RDA, recommended dietary allowance; T, tertile; T_1, first tertile; T_2, second tertile; T_3, third tertile; v, visit.

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Introduction

Growth differentiation factor 15 (GDF15), or macrophage inhibitory cytokine 1, is a stress response protein that has been linked to poor cognition [1,2] as well as other adverse health outcomes such as all-cause mortality in older populations [3–7] and diverse middle-aged adults [8]. GDF15 is secreted into the extracellular environment, and although it initially was identified as a member of the transforming growth factor β superfamily, it shares functional similarities with glial cell-derived neurotrophic factors (GDNFs) by binding to GDNF receptor-like proteins [9–12]. GDF15 is a pleiotropic factor that, depending on the cellular environment, can serve both positive and harmful purposes [13]. Circulating levels of GDF15 are usually elevated in response to stress, injury, and inflammation, as well as in homeostatic contexts such as energy and body weight management and pathological contexts such as cancer, cardiovascular disease, and other age-associated disorders [13–15]. GDF15 has been studied extensively in relation to inflammation and metabolism, and it has been identified in brain tissues, with accumulating evidence of it being involved in several neurological disorders. In animal studies, GDF15 is expressed in the central and peripheral nervous systems and secreted in the cerebrospinal fluid, where it can reach its target cells [16]. There is also evidence that is coexpressed with epidermal growth factor receptor (EGFR) in neural precursors to promote cell migration and proliferation [17]. Thus, knocking out GDF15 in the hippocampus may impair cognition [17].

The aging process is often accompanied by weight loss, fatigue, and multimorbidity, among others, often operationalized as frailty [8]. Frailty is a clinical syndrome that is classified as a decline in physiological reserve and an increased risk to stressors [18]. Although frailty is an age-associated clinical syndrome, it can commence at midlife and be a risk factor for disability, impairment in activities of daily living, and mortality [19,20]. Given the biological link of GDF15 with weight loss [12] and aging [21], it is plausible that serum GDF15 concentration may be associated with increased rates of frailty. Nevertheless, to date, no study has examined the role of GDF15 in the frailty process, particularly in middle-aged urban adults.

Furthermore, at both midlife and old age, frailty has been linked to poor diet assessed with various methods, though mostly focused on macro- and micronutrients rather than overall dietary quality [22–29]. In contrast, diets with high-quality scores based on alignment with the Healthy Eating Index (HEI), the Alternate HEI, and the Dietary Approaches to Stop Hypertension diet were associated with lower incidence of frailty [30–33]. At the same time, recent evidence suggests that diet quality was associated with reduced concentration of GDF15 [34]. However, the existence of synergism or antagonism between poor diet quality and elevation in GDF15 in determining increased risk for frailty has yet to be tested. Furthermore, these interactions may differ according to sociodemographic factors, such as sex and race.

Using prospective cohort data from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS), our study *1*) examined baseline GDF15 concentration in relation to incident frailty; *2*) tested super-multiplicative interactions between GDF15 concentration and various diet quality indices in relation to incidence of frailty; and *3*) assessed aim *1*) within both sex and race groups and aim *2*) across sex and race groups.

Methods

Database

Participants for this research project were selected from the HANDLS. HANDLS is a longitudinal, interdisciplinary, prospective cohort study of socioeconomically diverse White and African American adults living in Baltimore, MD, which commenced in 2004. Between 2004 and 2009, baseline data (visit 1; v1) were gathered through home visits, physical examinations, and a battery of cognitive tests on medical research vehicles (MRVs). Between 2009 and 2013 and then between 2013 and 2017, participants went to the MRVs for follow-up in-person visits (v2 and v3, respectively). Written informed consent was acquired from each subject. The HANDLS study protocol was approved by the institutional review board of the NIH National Institute of Environmental Health Sciences.

Study sample

The initial sample consisted of 3720 HANDLS participants. Of the $N = 3720$ initial sample, $n = 3050$ had available frailty scores at any of the 3 visits, of whom $n = 2901$ had diet quality scores at any of the 3 visits (Figure 1). Restricting this sample to those with complete v1 GDF15 serum concentration data resulted in a sample of $n = 945$ participants with 2247 observations. This sample was used to generate group-based trajectory model (GBTM) groups for diet quality indices. After longitudinally excluding individuals with a baseline event (i.e., frail or prefrail), incident frailty (frail or prefrail) was examined using Cox proportional hazards (PH) models on $n = 400$ participants with a follow-up time ≤13 y (604 observations, $n = 168$ failures [incidence of frail/prefrail status]).

Frailty status

The modified FRAIL scale, which is based on 5 domains—fatigue, resistance, ambulation, number of diseases, and weight loss—was used to assess frailty [35]. Details about the score calculations were reported previously [19]. From 0 to 5, scores could fall into one of 3 categories: nonfrail (score = 0), prefrail (score = 1

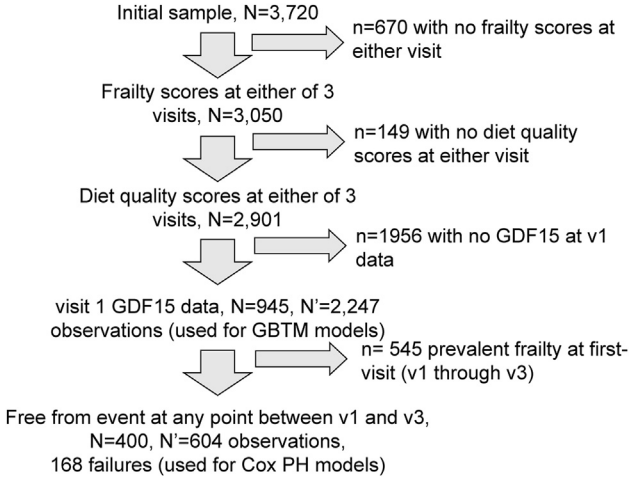

FIGURE 1. Participant flowchart: HANDLS 2004–2017. GBTM, group-based trajectory model; GDF15, growth differentiation factor 15; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; PH, proportional hazards.

or 2), or frail (score = 3,4, or 5). Frailty status was determined where possible at all 3 HANDLS visits, v1 (2004–2009), v2 (2009–2013), and v3 (2013–2017). Age at first event (being frail or prefrail) was determined in a time-dependent fashion, excluding individuals who were frail or prefrail at a prior visit from follow-up, starting from v1. Individuals were censored if they died prior to v3 or were lost to follow-up. The grouping into frail and prefrail together was done due to the expected small proportion of frailty incidence as detected in a previous larger sample of HANDLS [36]. Therefore, an analysis of frailty alone is expected to be underpowered, particularly with respect to examining interaction between diet and GDF15 exposures. Event date was determined by the date at examination in which an individual screened positive for frail or prefrail.

Measurement of serum GDF15 protein concentration

Blood samples were collected in the morning into BD Vacutainer serum separator tubes and then centrifuged at room temperature at 1142 × *g* for 15 min with the brake on. Serum was then aliquoted and stored at −80°C until use. The serum samples used in this study are from v1 of HANDLS. The Quantikine enzyme-linked immunosorbent assay kit (SGD150; R&D Systems) was used to measure serum GDF15 (pg/mL) according to the manufacturer's recommendations. Serum was thawed on ice and diluted 1:4 with calibrator diluent RD5-20. Diluted serum (50 μl) was used for the assay. Serum from 6 participants was combined to serve as controls, which were run in triplicate on each plate. We calculated the coefficient of variation (CV) for both the intra-assay and the interassay variability using these triplicate pooled serum samples. The intra- and interassay CVs were 4.78% and 9.95%, respectively. The GDF15 serum concentration was calculated based on a standard curve with recombinant GDF15. Assays were conducted blindly. More details regarding sample selection are provided elsewhere [8]. The values for GDF15 were $\log_e$-transformed (ln) for normalization purposes in all analyses. Moreover, tertiles (T_1, T_2, and T_3) were created, based on the final analytic sample distributions. In the main part of the analysis, T_3 was compared with combined T_1/T_2 to test interactions between poor diet quality trajectory groups.

Dietary assessment and diet quality indices

Dietary assessment

Two 24-h dietary recalls were collected at each of the 3 HANDLS visits (i.e., v1, v2, and v3), using the USDA Automated Multiple-Pass Method (AMPM), a well-established computerized structured interview [37]. Several measuring tools, such as measuring cups, spoons, rulers, and an illustrated food model booklet, were employed. These tools allowed participants to report the precise amounts of food and drink they had ingested. During the v1 study period (2004–2009), both recalls were administered in-person by professional interviewers, 4 to 10 d apart, whereas 1 of the 2 recalls was administered via telephone interview during the v2 and v3 study periods (2009–2013 and 2013–2017). The coding process of the dietary recall was carried out by trained nutrition professionals using Survey Net statistical software [37], which matches foods consumed with 8-digit codes identified in the Food and Nutrient Database for Dietary Studies version 3.0 for baseline visit v1 and version 5 for the follow-up visits v2 and v3 [38]. Three diet quality indices were generated from the dietary recalls as detailed below.

Diet quality indices

Healthy Eating Index-2010. The HEI-2010 was calculated for 24-h recall dietary data based on computational procedures and statistical code from the National Cancer Institute's Applied Research website [39], as described in depth previously for HANDLS data [40]. The overall and component HEI-2010 scores for each recall day (days 1 and 2) and each research visit were calculated. The mean HEI-2010 total and component scores were calculated by averaging food group and nutrient intake estimations for both recall days at each of the 3 HANDLS visits [41]. A higher HEI-2010 score represents a diet with better alignment to the Dietary Guidelines for Americans (DGA), which is considered a healthy diet. This version of HEI was used given that 2010 DGA was best suited to define diet quality at the time of the HANDLS study, particularly for the waves that were used in our present investigation.

Mean adequacy ratio. Methods that have been previously reported [42,43] were used to estimate the mean adequacy ratio (MAR) nutrient-based measure of diet quality. This second diet quality index was calculated using observed dietary intakes in relation to recommended dietary allowances (RDAs) for a number of vitamins and minerals, including calcium, magnesium, phosphorus, vitamins A, C, D, E, B-6, and B-12, folate, iron, thiamin, riboflavin, niacin, copper, zinc, and selenium. A nutrient adequacy ratio (NAR) was calculated from the RDAs and observed intake of each vitamin and mineral evaluated, as follows: NAR = actual daily nutrient intake for the subject divided by the RDA for that nutrient. Additionally, those who reported being current smokers had their RDA of vitamin C increased by 35 mg [44]. Following that, each NAR was converted to a percentage and truncated at 100% [43]. The MAR, a nutrient-based measure of overall dietary quality, was computed by summing all 17 nutrient NARs and dividing the sum by 17. Therefore, a higher score reflects a diet that adheres more closely to age- and sex-specific micronutrient requirements.

Dietary Inflammatory Index (DII). Thirty-five parameters were used to determine the inflammatory potential of the diet. Energy, alcohol, protein, carbohydrates, dietary fiber, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, ω-3 fatty acids, ω-6 fatty acids, cholesterol, 11 vitamins, 4 minerals, 6 flavonoid groups, caffeine, and tea were used to calculate the DII based on the initial computation of Shivappa et al. [45]. Trans fatty acids, garlic, ginger, onion, pepper, rosemary, saffron, thyme/oregano, turmeric, and eugenol were excluded. Their omission would not have a significant association with the predictive ability of the DII score since they are consumed in small quantities by the United States population [45]. The calculation of the DII score was based on dietary intake data from 2 24-h recalls that were linked to the regionally representative world database. The global composite database represented diets of diverse populations residing in several countries in different regions of the word including but not limited to the United States, Japan, Australia, Korea, Mexico, India, Taiwan, United Kingdom, and New Zealand. For each participant, a *z*-score and centered percentile was based on the global estimate of the mean and SD

of each DII parameter [45]. The centered percentile value for each food parameter was multiplied by the overall food parameter-specific inflammatory effect score [45] to obtain the food parameter-specific DII score. All the food parameter-specific DII scores were summed to create the overall DII score for an individual. Using data from the HANDLS study and the global composite database [45], the maximum proinflammatory and anti-inflammatory DII scores were calculated as +10.44 and −10.44, respectively. The more proinflammatory the dietary pattern, the higher the DII score.

GBTMs for diet quality indices. Part of the descriptive analyses was conducted on visits 1 through 3 diet quality indices. However, the main analyses were carried out on trajectories that were estimated using GBTMs. Diet quality trajectories were created using data from all 3 visits and the Stata plugins *traj* and *trajplot* for predicting GBTM [46,47]. The plugin is an adaptation of a well-known SAS procedure [46] that detects groups of people with comparable long-term developmental paths. In this group-based approach, model parameters are estimated using a multinomial modeling strategy and maximum likelihood, with optimization accomplished using the quasi-Newton procedure. We exhibited group-based trajectories over time with 95% confidence intervals (CIs) and defined a censored normal distribution for the chosen outcomes, with intercept (0), linear (1), quadratic (2), and cubic (3) orders for each group trajectory. For consistency and readability, we established ≤3 groups for each dietary quality index. Increasing the number of groups was additionally attempted. However, given that the estimated prevalence of these additional groups was <5% in some of these diet quality indices, only 3 groups were selected. We examined the Bayesian information criterion (BIC) for each GBTM model as a goodness-of-fit measure. Alternative models were compared per diet quality index using a difference in BIC cutoff of 20 points, deciding on the most parsimonious model possible. The linear model was selected when ΔBIC was smaller than the quadratic model by a number >20. All 3 diet quality indices underwent this process, with age as the time variable in these models. Consequently, each index yielded trajectories for 3 groups. Intercept and slope estimates with *P* values from the GBTMs were calculated for each group to determine their respective labels. In addition, visit-specific mean ± SD of each diet quality index were also calculated per GBTM group.

Covariates

We included additional covariates selected for their prior association with frailty, namely baseline measures of age (continuous, years), sex (male, female), race (White = 0, African American = 1), poverty status (below = 1, above = 0 the 125% the federal poverty line), and educational attainment (less than high school, high school, more than high school). In addition, we included nondietary behavioral characteristics, mainly current smoking status (0 = No, 1 = Yes), illicit drug use (0 = No, 1 = Yes, using any marijuana, opiates, and/or cocaine) among potential confounders.

Statistical methods

All analyses were completed using Stata release 18 [48]. Covariates (aside from main exposures and effect modifiers) with missing data in the analyses were imputed using chained equations with 5 imputations and 10 iterations. First, we described the study sample's characteristics overall and across sex and racial groups, comparing means and proportions with bivariate linear, logistic, and multinomial logit models. Second, we explored the association of GDF15 tertiles and GBTM groups of diet quality indices with probability of remaining nonfrail, using Kaplan–Meier survival curves and log-rank tests. Scatterplot matrices of ln(GDF15) measured at v1 and v1 diet quality indices were also displayed. Third, to test our key hypotheses, we fitted several Cox PH models, with the event of interest being incident frailty (frail or prefrail) between v1 age and follow-up age included in person–period format. Participants were censored at age of event, age at death, or loss to follow-up, or age at end of follow-up, whichever came first. In the first set of analyses (*Analysis A*), diet quality indices were only entered as main effects along with the exposure and other covariates. The main exposure was GDF15 serum concentration, measured as categorical tertiles after ln transformation, comparing T_3 or T_2 to the common referent category T_1. The 3 GBTM grouped diet quality indices (HEI-2010, DII, and MAR) were coded in order of higher diet quality and entered as categorical variables separately in each model. In the second set of analyses (*Analysis B*), a 2-way interaction term was added between GDF15 serum concentration (ln-transformed, T_3 compared with T_1/T_2 combined) and each of the 3 diet quality indices separately, comparing "low" to "medium/high" diet quality groups. Two alternative models were tested, with Model 1 including only age, sex, race, and poverty status, whereas Model 2 additionally adjusted for education, current smoking status, and current drug use. All analyses were also stratified by sex and by race. Further stratification within sexes and racial groups by diet quality trajectory groups was performed as a secondary analysis for ease of interpretation. Type I error rate for this study was set a priori for main and interactive associations before correcting for multiple testing to 0.05 and 0.10, respectively [49]. After familywise Bonferroni correction, accounting for the main exposures of interest, they were reduced to 0.05/4 = 0.0125 and 0.10/4 = 0.025, respectively, as in previous studies [50].

Results

Figure 2 shows main GBTM findings through trajectory plots for HEI-2010, DII, and MAR and labeling of the trajectories according to ascending order of dietary quality, from low to high. Slopes and intercepts associated with each of the GBTM groups and for each diet quality index are provided in Supplemental Results 1. Generally, the lowest diet quality groups accounted for 56.5% of the sample in the case of HEI-2010, with a lower prevalence in the case of DII (40.5%) and MAR (30.5%). The latter had the largest portion labeled as "high diet quality" (26.6%) compared with the other 2 diet quality indices (4.7% for HEI-2010, 10.8% for DII).

Table 1 displays study sample characteristics by sex and race, focusing on the initial selected sample for GBTM analysis (n = 945). ln(GDF15), measured at v1, was higher among males, whereas females were more likely than males to be frail or prefrail at each visit. Both sex and racial differences were noted for diet quality trajectories, with females generally having better diet quality than males and belonging to the "high diet quality" trajectory being more probable among White adults compared to

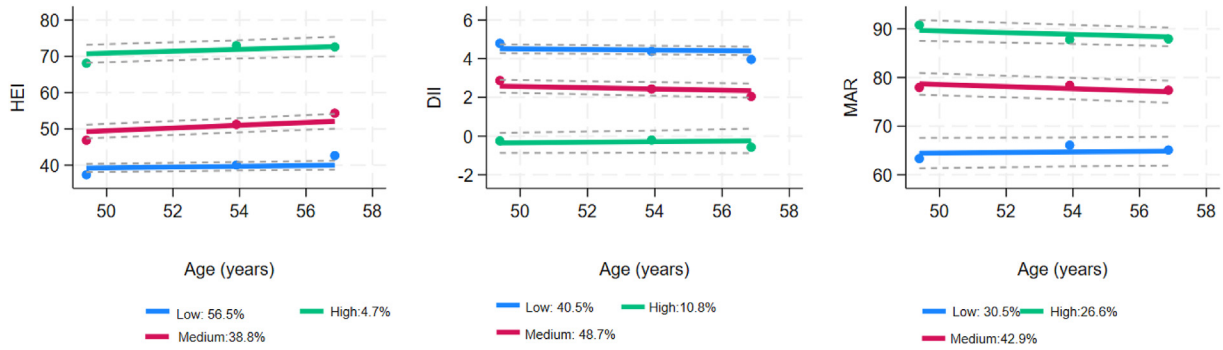

FIGURE 2. Group-based trajectory model findings for diet quality indices: HANDLS 2004–2017.[1] DII, Dietary Inflammatory Index; GBTM, group-based trajectory model; HEI, Healthy Eating Index; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; MAR, mean adequacy ratio. [1]Diet quality trajectories are grouped as high, medium, and low, as follows: green = "high diet quality"; red = "medium diet quality"; blue = "low diet quality." Percentages are mean predicted probabilities from the GBTM model for each group and each diet quality index.

African American adults. Current drug and tobacco use was also more prevalent among male and African American adults compared to female and White adults, respectively, as was the proportion living below poverty and having less than high school educational attainment.

Figure 3 shows a series of Kaplan–Meier curves for the probability of remaining nonfrail against levels of diet quality trajectories and GDF15 concentration tertiles along with a log-rank test. Overall, 168 events (incidence of frail/prefrail) occurred over the follow-up period in 400 frailty-free subjects at first visit, with 604 observations in person–period format. Importantly, both elevated GDF15 serum concentration, particularly T_3 compared with T_1, and lower diet quality trajectories were associated with a lower probability of remaining nonfrail over a follow-up period of 13 y. Log-rank tests indicated significant differences in survival probabilities. In addition, the scatterplot matrix indicated that GDF15 is moderately but inversely related to diet quality at v1, by being inversely associated with HEI-2010 and MAR and positively associated with the raw DII score.

In contrast, Table 2 examines the association of ln(GDF15) with incidence of frailty (frail or prefrail) using a series of Cox PH models in which adjustment was made alternatively for HEI-2010, DII, and MAR trajectories. In the reduced models that adjusted for age, sex, race, and poverty status, ln(GDF15), when comparing T_3 with T_1, was directly associated with the incidence of frailty (frail or prefrail), particularly in models adjusted for the MAR trajectories. This association remained statistically significant after further adjustment for education, current smoking, and drug use in Model 2. Nevertheless, in stratified analyses by sex and by race alternatively, this strong positive association was only detected among males in the reduced model. In contrast, a "high diet quality" DII trajectory was consistently associated with reduced risk of frailty over time, when comparing high with low diet quality trajectory groups, including among males, females, White, and African American adults. A similar pattern was observed for HEI-2010 and MAR, although this was only consistent in the overall sample in the reduced models. Most notably, among females and in the fully adjusted model, the "high diet quality" HEI-2010 trajectory when compared with the "low diet quality" trajectory group had a hazard ratio (HR) of 0.15 (95% CI: 0.04, 0.54, $P = 0.004$). This association was not detected in males and White or African American adults.

The interaction between low diet quality and elevated GDF15 serum concentration in relation to frailty incidence was tested through a similar series of Cox regression models adjusted for key potential confounders, and the results presented in Table 3. Stratified models presenting HRs with 95% CIs for elevated GDF15 serum concentration in relation to frailty risk across diet quality trajectory groups are shown separately in Table 4, in males, females, and White and African American adults.

In males only, there was an antagonistic interaction between low diet quality and elevated GDF15 serum concentration whereby the association of elevated GDF15 on frailty was stronger in higher diet quality trajectory groups, although this was only found for HEI-2010. This interaction can be interpreted as a difference in ln(HR)s of elevated GDF15 in relation to frailty risk between the lower HEI-2010 trajectory and the group with medium/high HEI-2010 trajectory. Therefore, it is estimated from the stratified model (Table 4) that the HR for GDF15-frailty in the higher diet quality group, and in males, was 2.69 (95% CI: 1.10, 6.60; $P = 0.032$), whereas among the lower diet quality group, the HR was 0.94 (95% CI: 0.49, 1.79; $P = 0.86$). Similarly, the association of low diet quality with frailty in males was more pronounced at a lower GDF15 serum concentration (T_1 and T_2). In this instance, low diet quality (HEI-2010, T_1 compared with T_2/T_3 combined) was associated with frailty with an HR of 2.03 (95% CI: 1.16, 3.80; $P = 0.027$) in the subgroup with lower GDF15 (T_1 and T_2 combined), whereas among the elevated GDF15 group (T_3), the estimated HR was 0.82 (95% CI: 0.35, 1.94; $P = 0.65$) (data not shown).

It also is worth noting that based on Table 4 stratified analyses findings, GDF15 (T_3 compared with both T_1/T_2 combined) was independently associated with frailty incidence in African American adults in all models, particularly at higher diet quality trajectories, even though no heterogeneity across levels of diet quality trajectory groups was detected in Table 3. For instance, within the higher diet quality group based on HEI-2010 (Table 4), elevated GDF15 serum concentration was associated with 2.97-fold ($P = 0.011$, reduced Model 1) increase in frailty risk. This association within the higher diet quality group remained statistically significant in the fully adjusted Model 2 (Table 4) and passing familywise Bonferroni correction for HEI-2010 and MAR. Most discussed associations in Tables 2–4 above passed familywise Bonferroni correction.

TABLE 1
Study sample characteristics by sex and by race: HANDLS 2004–2017[1]

	Overall	Female	Male	White	African American	*P*-sex[2]	*P*-race[2]
	(X or % ± SE)	(X or % ± SE)	(X or % ± SE)	(X or % ± SE)	(X or % ± SE)		
	(*N* = 945)	(*N* = 505)	(*N* = 440)	(*N* = 408)	(*N* = 537)		
X ± SE or % ± SE							
GDF15 at v1, pg/mL							
log_e transformed, ln	6.52 ± 0.02	6.45 ± 2.8	6.60 ± 0.03	6.50 ± 0.03	6.54 ± 3.0	0.001	0.36
T_1: 4.43–6.17	31.3 ± 1.5	34.7 ± 2.1	27.5 ± 2.1	30.9 ± 2.0	31.7 ± 2.0	0.005	0.83
T_2: 6.18–6.67	31.6 ± 1.5	32.1 ± 2.1	31.1 ± 2.2	31.9 ± 2.3	31.5 ± 2.0	0.12	0.99
T_3: 6.67–9.33	37.0 ± 1.6	33.3 ± 2.1	41.4 ± 2.3	37.3 ± 2.4	36.9 ± 2.1	Ref	Ref
Baseline sociodemographic, SES, and health-related variables							
Sex, % male	46.6 ± 1.6	0.0	100.0	47.3 ± 2.5	46.0 ± 2.2	_	0.69
Age at v1, y	49.4 ± 0.3	49.4 ± 0.4	49.5 ± 0.4	49.7 ± 0.5	49.2 ± 0.4	0.88	0.41
African American, %	56.8 ± 1.6	57.4 ± 2.2	56.1 ± 2.4	0.0	100.0	0.69	_
Poverty status, % <125% of the 2004 federal poverty guidelines	42.9 ± 1.6	45.9 ± 2.2	39.3 ± 2.3	35.8 ± 2.4	48.2 ± 2.1	0.040	<0.001
Education, completed, %							
<HS	6.6 ± 0.8	4.8 ± 1.0	8.7 ± 1.3	9.8 ± 1.5	4.2 ± 0.9	0.032	<0.001
HS	59.0 ± 1.6	59.1 ± 2.2	58.9 ± 2.4	50.9 ± 2.5	65.1 ± 2.1	Ref	Ref
>HS	34.4 ± 1.5	36.1 ± 2.2	32.5 ± 2.2	39.3 ± 2.4	30.7 ± 2.0	0.47	<0.001
Baseline drug and tobacco use							
Any drug, current user, %	19.1 ± 1.4	14.4 ± 1.8	24.5 ± 2.1	13.2 ± 1.7	23.6 ± 2.0	0.001	<0.001
Tobacco, current user, %	49.5 ± 1.7	43.6 ± 2.3	56.4 ± 2.4	42.9 ± 2.5	54.6 ± 2.2	<0.001	<0.001
Frailty status at v1	*N* = 931	*N* = 497	*N* = 434	*N* = 404	*N* = 527		
Nonfrail	51.0 ± 1.6	42.9 ± 2.2	60.4 ± 2.3	52.7 ± 2.5	49.7 ± 2.2	Ref	Ref
Prefrail	36.1 ± 1.6	40.8 ± 2.2	30.6 ± 2.2	31.7 ± 2.3	39.5 ± 2.1	<0.001	0.055
Frail	12.9 ± 1.1	16.3 ± 1.7	9.0 ± 1.4	15.6 ± 1.8	10.8 ± 1.4	<0.001	0.13
Frailty status at v2	*N* = 552	*N* = 303	*N* = 249	*N* = 250	*N* = 302		
Nonfrail	46.9 ± 2.1	40.3 ± 2.8	55.0 ± 3.1	45.6 ± 3.2	48.0 ± 2.9	Ref	Ref
Prefrail	37.7 ± 2.1	38.6 ± 2.8	36.5 ± 3.1	37.6 ± 3.1	37.7 ± 2.8	0.050	0.80
Frail	15.4 ± 1.5	21.1 ± 2.3	8.4 ± 1.8	16.8 ± 2.4	14.2 ± 2.0	<0.001	0.39
Frailty status at v3	*N* = 564	*N* = 326	*N* = 238	*N* = 241	*N* = 323		
Nonfrail	50.2 ± 2.1	45.7 ± 2.8	56.3 ± 3.2	47.7 ± 3.2	52.0 ± 2.8	Ref	Ref
Prefrail	33.9 ± 2.0	35.0 ± 2.6	32.4 ± 3.0	36.0 ± 3.1	32.2 ± 2.6	0.13	0.29
Frail	16.0 ± 1.5	19.3 ± 2.2	11.3 ± 2.0	16.2 ± 2.4	15.8 ± 2.0	0.004	0.65
HEI-2010 diet quality trajectory							
Low	61.9 ± 1.6	57.2 ± 2.2	67.3 ± 2.2	61.3 ± 2.4	62.4 ± 2.1	Ref	Ref
Medium	33.7 ± 1.5	37.2 ± 2.2	29.5 ± 2.2	32.4 ± 2.3	34.6 ± 2.1	0.005	0.72
High	4.4 ± 0.7	5.5 ± 1.0	3.2 ± 0.8	6.4 ± 1.2	3.0 ± 0.7	0.034	0.018
DII diet quality trajectory							
Low	43.6 ± 1.6	49.7 ± 2.2	36.6 ± 2.2	39.2 ± 2.4	46.9 ± 2.2	<0.001	0.22
Medium	47.5 ± 1.6	43.6 ± 2.2	52.0 ± 2.4	47.3 ± 2.5	47.7 ± 2.2	Ref	Ref
High	8.8 ± 0.9	6.7 ± 1.1	11.4 ± 1.5	13.5 ± 1.6	5.4 ± 1.0	0.15	<0.001
MAR diet quality trajectory							
Low	24.3 ± 1.4	31.9 ± 2.1	15.7 ± 1.7	19.9 ± 2.0	27.7 ± 1.9	<0.001	0.087
Medium	46.6 ± 1.6	44.8 ± 2.2	48.6 ± 2.4	45.3 ± 2.5	47.5 ± 2.2	Ref	Ref
High	29.1 ± 1.5	23.4 ± 1.9	35.7 ± 2.3	34.8 ± 2.4	24.8 ± 1.9	0.028	0.012

Abbreviations: DII, Dietary Inflammatory Index; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; HEI-2010, Healthy Eating Index, 2010 revision; HS, high school; ln, natural logarithm; MAR, mean adequacy ratio; Ref, reference; *N*, number of participants; SD, standard deviation; SE, standard error; T, tertile; T_1, first tertile; T_2, second tertile; T_3, third tertile; v, visit.

[1] Values are mean (X) ± SE for continuous variables and % for categorical variables. See Figure 1 for participant flowchart. One SD of ln(GDF15) is equivalent to a value of 0.669.

[2] *P* for null hypothesis that $\beta = 0$ from models that included sex or race as the only predictors. Models were ordinary least squares linear regression models for continuous variables and multinomial logit models for categorical variables, applied to multiple imputed data.

Discussion

Main findings

This study examined whether elevated GDF15 and poor diet quality interact in relation to the risk of frailty in middle-aged urban adults. The study found that both elevated GDF15 and lower diet quality trajectories were associated with a lower probability of remaining nonfrail over a follow-up period of ≤13 y. Among females and in the fully adjusted model, the "high diet quality" HEI-2010 trajectory group, when compared with the "low diet quality" trajectory group, had a significantly lower risk. In males only, there was an antagonistic interaction between low

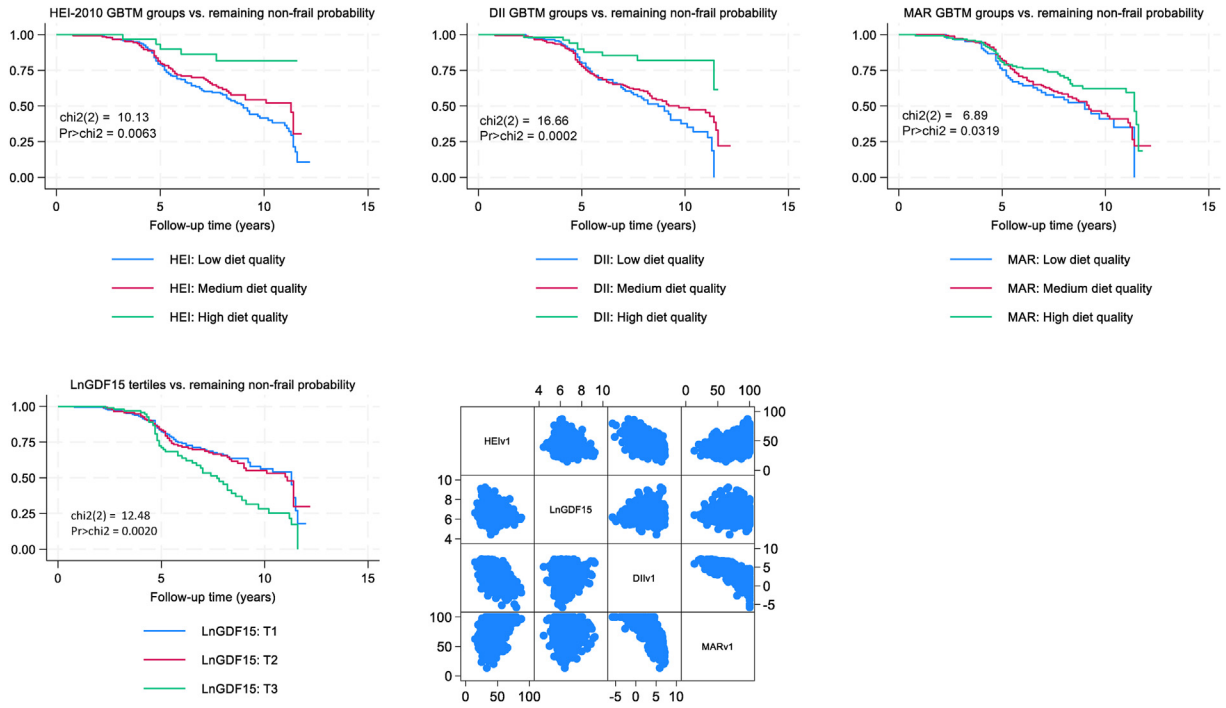

FIGURE 3. Association between trajectories of diet quality indices, ln(GDF15) tertiles, and probability of remaining nonfrail: Kaplan–Meier survival curves and scatterplot matrix, HANDLS 2004-2017.[1,2] DII, Dietary Inflammatory Index; GBTM, group-based trajectory model; GDF15, growth differentiation factor 15; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; HEI, Healthy Eating Index; MAR, mean adequacy ratio. [1]Diet quality trajectories are grouped as high, medium, and low, as follows: green = "high diet quality"; red = "medium diet quality"; blue = "low diet quality." [2]Scatterplot matrices are shown for descriptive purposes between baseline diet quality indices and ln(GDF15).

diet quality (lower HEI-2010 trajectory) and elevated GDF15. Specifically, the HR for GDF15–frailty in the higher diet quality trajectory group (high/medium combined), and in males, was 2.69 (95% CI: 1.06, 6.62; $P = 0.032$), whereas in the lower diet quality trajectory group, the HR was 0.94 (95% CI: 0.49, 1.80; $P = 0.86$). GDF15 was independently associated with frailty in African American adults.

Previous studies

GDF15 and frailty

Frailty often results in a progressive loss of homeostasis, reduced physiological reserve and resilience, and increased vulnerability to stress [18]. Here, we report that higher GDF15 was associated with the probability of becoming frail. These data are in agreement with other reports showing that GDF15 was higher in frail ($n = 28$) compared with nonfrail ($n = 27$) older adults (>64 y) in Chile [51]. In a cross-sectional analysis from the Multidomain Alzheimer Preventive Trial of White elderly (>70 y, $n = 1199$) adults in France, higher GDF15 was reported in individuals who were frail as a result of a disease than in individuals with age-related frailty or nonfrail individuals [52]. In their study, there were no differences in GDF15 between nonfrail and age-related frail individuals [52]. GDF15 was positively associated with the frailty index in a community-based sample (age 20–90 y; $n = 280$) and in older adults undergoing surgery [53]. In their study, GDF15, along with 6 other inflammatory markers, predicted adverse postsurgical outcomes [53]. Our finding that GDF15 at midlife was associated with frailty later in life is also consistent with other studies that found that other inflammatory markers, including C-reactive protein (CRP) [54] or CRP and 4 other inflammatory markers [55], were associated with frailty later in life. These data suggest that elevated GDF15 is associated with increased risk for frailty. Our results demonstrated that T_3 of GDF15 had a significant greater risk of frailty compared to T_1, potentially suggesting that there may be some clinical GDF15 threshold, which in our study corresponded to 1103 pg/mL, approximately the median of T_3, to consider for predicting frailty risk. However, future studies would need to explore a similar association and replicate this finding, which could serve important clinical and diagnostic roles.

Diet quality and frailty

Poor nutritional status is recognized as a key contributor to the pathophysiology of frailty [56]. Each diet quality measure used in this study had similar yet unique pathophysiological links to frailty. The DII is associated with inflammatory status, HEI represents overall diet quality measured by alignment with DGA recommendations to promote health and prevent disease, and MAR reflects micronutrient intake compared to recommended allowances. The similar associations between high-quality diets, regardless of the index, and frailty most likely result from the incorporation of key nutrients and dietary components such as antioxidants, polyphenols, and dietary fiber provided by these diets [26,33].

Diet quality, GDF15, and frailty

In this study, we found differences in the relationship between GDF15, diet quality, and frailty. In males, low HEI-2010 diet quality was associated with elevated GDF15, but the association between elevated GDF15 and frailty was stronger with better diet quality. However, in females, the association between GDF15 and frailty was further strengthened with low HEI-2010 diet quality trajectory. Few studies have examined the

TABLE 2
ln(GDF15) tertiles, diet quality trajectory groups, and frailty incidence: Cox proportional hazards models: HANDLS 2004–2017[1]

	Overall		Female		Male		White		African American	
	β ± SE	*P*	β ± SE	*P*	β ± SE	*P*	β ± SE	*P*	β ± SE	*P*
	(N' = 604, N = 400)		(N' = 286, N = 184)		(N' = 318, N = 216)		(N' = 254, N = 174)		(N' = 350, N = 226)	
HEI-2010										
Model 1										
GBTM group 2 vs. group 1: medium vs. low	−0.202 ± 0.174	0.25	+0.021 ± 0.240	0.93	−0.359 ± 0.263	0.17	−0.526 ± 0.286	0.066	+0.134 ± 0.225	0.55
GBTM group 3 vs. group 1: high vs. low	−1.495 ± 0.474	0.002[2]	−1.625 ± 0.625	0.009[2]	−0.731 ± 0.743	0.33	−1.444 ± 0.576	0.012	−1.639 ± 1.012	0.11
ln(GDF15)										
T_2 vs. T_1	−0.012 ± 0.199	0.95	−0.409 ± 0.284	0.15	+0.470 ± 0.305	0.12	+0.271 ± 0.297	0.36	−0.381 ± 0.273	0.16
T_3 vs. T_1	0.439 ± 0.231	0.058	+0.527 ± 0.330	0.11	+0.637 ± 0.352	0.070	+0.424 ± 0.368	0.25	+0.460 ± 0.296	0.12
Model 2										
GBTM group 2 vs. group 1: medium vs. low	−0.175 ± 0.180	0.33	−0.059 ± 0.255	0.82	−0.249 ± 0.274	0.37	−0.419 ± 0.308	0.17	+0.083 ± 0.231	0.72
GBTM group 3 vs. group 1: high vs. low	−1.460 ± 0.490	0.003[2]	−1.914 ± 0.662	0.004[2]	−0.557 ± 0.756	0.46	−1.247 ± 0.639	0.051	−1.672 ± 1.02	0.10
ln(GDF15)										
T_2 vs. T_1	−0.015 ± 0.209	0.95	−0.342 ± 0.304	0.26	+0.346 ± 0.318	0.28	+0.203 ± 0.315	0.52	−0.405 ± 0.284	0.15
T_3 vs. T_1	+0.456 ± 0.247	0.064	+0.656 ± 0.347	0.059	+0.510 ± 0.382	0.18	+0.400 ± 0.393	0.310	+0.489 ± 0.318	0.12
DII										
Model 1										
GBTM group 2 vs. group 1: medium vs. low	−0.244 ± 0.168	0.15	−0.241 ± 0.225	0.29	−0.217 ± 0.255	0.39	−0.136 ± 0.260	0.60	−0.248 ± 0.222	0.26
GBTM group 3 vs. group 1: high vs. low	−1.423 ± 0.372	<0.001[2]	−1.661 ± 0.644	0.010[2]	−1.117 ± 0.469	0.017	−1.282 ± 0.466	0.006[2]	−1.575 ± 0.739	0.033
ln(GDF15)										
T_2 vs. T_1	−0.016 ± 0.199	0.94	−0.438 ± 0.284	0.12	+0.478 ± 0.301	0.39	+0.288 ± 0.298	0.34	−0.382 ± 0.274	0.16
T_3 vs. T_1	0.468 ± 0.230	0.041	+0.482 ± 0.322	0.13	+0.659 ± 0.348	0.058	+0.528 ± 0.357	0.14	+0.460 ± 0.295	0.12
Model 2										
GBTM group 2 vs. group 1: medium vs. low	−0.222 ± 0.171	0.19	−0.262 ± 0.231	0.26	−0.165 ± 0.261	0.53	−0.108 ± 0.268	0.69	−0.246 ± 0.224	0.27
GBTM group 3 vs. group 1: high vs. low	−1.385 ± 0.384	<0.001[2]	−1.920 ± 0.675	0.004[2]	−0.986 ± 0.483	0.041	−1.122 ± 0.505	0.026	−1.665 ± 0.742	0.025
ln(GDF15)										
T_2 vs. T_1	−0.029 ± 0.208	0.89	−0.417 ± 0.299	0.16	+0.350 ± 0.316	0.27	+0.221 ± 0.314	0.48	−0.396 ± 0.285	0.16
T_3 vs. T_1	+0.470 ± 0.246	0.056	+0.602 ± 0.343	0.080	+0.520 ± 0.381	0.17	+0.479 ± 0.388	0.22	+0.490 ± 0.318	0.12
MAR										
Model 1										
GBTM group 2 vs. group 1: medium vs. low	−0.196 ± 0.196	0.32	−0.203 ± 0.253	0.42	−0.241 ± 0.326	0.46	+0.251 ± 0.337	0.46	−0.142 ± 0.243	0.56
GBTM group 3 vs. group 1: high vs. low	−0.600 ± 0.230	0.009[2]	−0.682 ± 0.332	0.040	−0.546 ± 0.350	0.12	−0.578 ± 0.367	0.12	−0.576 ± 0.322	0.074
ln(GDF15)										
T_2 vs. T_1	+0.025 ± 0.200	0.90	−0.440 ± 0.287	0.13	+0.531 ± 0.300	0.076	+0.383 ± 0.298	0.20	−0.399 ± 0.276	0.15
T_3 vs. T_1	+0.539 ± 0.229	0.018	+0.529 ± 0.319	0.098	+0.750 ± 0.346	0.030	*+0.645 ± 0.360*	*0.073*	+0.478 ± 0.294	0.10
Model 2										
GBTM group 2 vs. group 1: medium vs. low	−0.220 ± 0.197	0.27	−0.232 ± 0.261	0.38	−0.224 ± 0.331	0.50	−0.170 ± 0.341	0.62	−0.156 ± 0.247	0.53
GBTM group 3 vs. group 1: high vs. low	−0.586 ± 0.231	0.011[2]	−0.726 ± 0.340	0.033	−0.491 ± 0.354	0.17	−0.408 ± 0.376	0.28	−0.653 ± 0.328	0.047
ln(GDF15)										
T_2 vs. T_1	−0.022 ± 0.208	0.92	−0.422 ± 0.302	0.16	+0.368 ± 0.314	0.24	+0.239 ± 0.316	0.45	−0.427 ± 0.286	0.14
T_3 vs. T_1	+0.482 ± 0.245	0.049	+0.553 ± 0.338	0.10	+0.543 ± 0.383	0.16	0.512 ± 0.390	0.19	+0.476 ± 0.318	0.13

Abbreviations: DII, Dietary Inflammatory Index; GBTM, group-based trajectory model; GDF15, growth differentiation factor 15; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; HEI-2010, Healthy Eating Index, 2010 revision; ln, natural logarithm; MAR, mean adequacy ratio; N = number of participants; N' = number of observations in person–period format; SE, standard error; T, tertile; T_1, first tertile; T_2, second tertile; T_3, third tertile.

[1] Values are ln(HR) for main effects of diet quality trajectories comparing medium to low and high to low and main effects of ln(GDF15) comparing T_3 to T_1 and T_2 to T_1. See ranges of ln(GDF15) tertiles in Table 1.

[2] $P < 0.05$ after familywise Bonferroni correction (type I error adjusted to 0.0125 for main effects and 0.025 for 2-way interaction terms).

TABLE 3

Interactions between GDF15H [elevated ln(GDF15) (T_3 vs. T_1/T_2)] and LDQT (low diet quality trajectory vs. medium/high) in relation to frailty incidence: Cox proportional hazards models, HANDLS 2004–2017[1]

	Overall		Female		Male		White		African American	
	β ± SE	*P*	β ± SE	*P*	β ± SE	*P*	β ± SE	*P*	β ± SE	*P*
	(N' = 604, N = 400)		(N' = 286, N = 184)		(N' = 318, N = 216)		(N' = 254, N = 174)		(N' = 350, N = 226)	
HEI-2010										
Model 1										
LDQT	+0.490 ± 0.197	0.013	+0.145 ± 0.270	0.59	+0.781 ± 0.310	0.012[2]	+0.815 ± 0.307	0.008[2]	+0.081 ± 0.260	0.76
GDF15H	+0.824 ± 0.326	0.011[2]	+0.456 ± 0.545	0.40	+1.148 ± 0.432	0.002[2]	+0.680 ± 0.567	0.23	+0.899 ± 0.402	0.025
LDQT × GDF15H	−0.519 ± 0.378	0.17	+0.418 ± 0.620	0.50	−1.173 ± 0.507	0.021[2]	−0.590 ± 0.629	0.35	−0.301 ± 0.482	0.53
Model 2										
LDQT	+0.424 ± 0.208	0.042	+0.211 ± 0.292	0.47	+0.621 ± 0.326	0.057	+0.577 ± 0.363	0.11	+0.120 ± 0.264	0.65
GDF15H	+0.777 ± 0.335	0.020	+0.544 ± 0.557	0.33	+1.027 ± 0.441	0.020	+0.472 ± 0.597	0.43	+0.914 ± 0.412	0.027
LDQT × GDF15H	−0.458 ± 0.383	0.23	+0.316 ± 0.632	0.62	−1.148 ± 0.529	0.030	−0.324 ± 0.672	0.63	−0.253 ± 0.486	0.60
DII										
Model 1										
LDQT	+0.479 ± 0.199	0.016	+0.405 ± 0.267	0.13	+0.579 ± 0.310	0.063	+0.425 ± 0.323	0.19	+0.407 ± 0.261	0.12
GDF15H	+0.643 ± 0.235	0.006[2]	+0.904 ± 0.395	0.022	+0.529 ± 0.297	0.075	+0.496 ± 0.353	0.16	+0.790 ± 0.317	0.013
LDQT × GDF15H	−0.302 ± 0.345	0.38	−0.184 ± 0.507	0.72	−0.596 ± 0.505	0.24	−0.303 ± 0.519	0.56	−0.239 ± 0.469	0.61
Model 2										
LDQT	+0.433 ± 0.203	0.033	+0.430 ± 0.275	0.12	+0.478 ± 0.319	0.13	+0.256 ± 0.339	0.45	0.450 ± 0.263	0.088
GDF15H	+0.619 ± 0.243	0.011[2]	+0.967 ± 0.414	0.020	+0.405 ± 0.311	0.19	+0.386 ± 0.366	0.29	+0.872 ± 0.332	0.009
LDQT × GDF15H	−0.316 ± 0.346	0.36	−0.264 ± 0.519	0.61	−0.600 ± 0.512	0.24	−0.188 ± 0.526	0.72	−0.302 ± 0.476	0.53
MAR										
Model 1										
LDQT	+0.375 ± 0.221	0.090	+0.381 ± 0.283	0.18	+0.512 ± 0.364	0.16	0.385 ± 0.413	0.35	+0.346 ± 0.267	0.20
GDF15H	+0.577 ± 0.213	0.007[2]	+0.846 ± 0.346	0.015	+0.457 ± 0.278	0.10	0.400 ± 0.319	0.21	+0.792 ± 0.292	0.007[2]
LDQT × GDF15H	−0.138 ± 0.406	0.734	−0.105 ± 0.527	0.84	−0.511 ± 0.715	0.48	−0.022 ± 0.646	0.97	−0.288 ± 0.542	0.60
Model 2										
LDQT	+0.368 ± 0.222	0.097	+0.400 ± 0.291	0.17	+0.505 ± 0.370	0.17	+0.270 ± 0.422	0.52	+0.348 ± 0.269	0.20
GDF15H	+0.522 ± 0.222	0.019	+0.400 ± 0.378	0.030	+0.332 ± 0.294	0.26	+0.334 ± 0.335	0.32	+0.818 ± 0.310	0.008[2]
LDQT × GDF15H	−0.083 ± 0.412	0.84	−0.085 ± 0.551	0.88	−0.621 ± 0.733	0.40	−0.068 ± 0.675	0.92	−0.210 ± 0.554	0.71

Abbreviations: DII, Dietary Inflammatory Index; GDF15, growth differentiation factor 15; GDF15H, high $\log_e$-transformed GDF15 (T3 vs. T1/T2); HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; HEI, Healthy Eating Index; HR, hazard ratio; LDQT, low diet quality trajectory; ln, natural logarithm; MAR, mean adequacy ratio; N, number of participants; N' = number of observations in person–period format; SE, standard error; T, tertile; T_1, first tertile; T_2, second tertile; T_3, third tertile.

[1] Values are ln(HR) for main effects of LDQT, GDF15H, and 2-way interaction between the 2 variables.

[2] $P < 0.05$ after familywise Bonferroni correction (type I error adjusted to 0.0125 for main effects and 0.025 for 2-way interaction terms).

TABLE 4
GDF15H in relation to frailty incidence across diet quality trajectory groups (LDQT vs. MHDQT): Cox proportional hazards models: HANDLS 2004–2017[1]

		HEI-2010					DII					MAR				
		N′	HR	LCL	UCL	*P*	*N′*	HR	LCL	UCL	*P*	*N′*	HR	LCL	UCL	*P*
Model 1: Reduced																
Females	MHDQT	153	1.57	0.53	4.66	0.42	165	2.10	0.92	4.79	0.077	208	2.25	1.08	4.71	0.031
Females	LDQT	133	1.87	0.91	3.82	0.086	121	2.23	1.04	4.80	0.039	78	1.91	0.81	4.51	0.14
Males	MHDQT	128	2.69	1.10	6.60	0.031[3]	233	1.65	0.90	3.03	0.1	274	1.57	0.90	2.75	0.11
Males	LDQT	190	0.94	0.49	1.79	0.86	85	0.79	0.30	2.12	0.65	44	0.43	0.08	2.38	0.33
White	MHDQT	129	1.80	0.62	5.18	0.32	191	1.49	0.72	3.06	0.28	225	1.29	0.68	2.45	0.44
White	LDQT	125	1.20	0.59	2.46	0.61	63	1.38	0.54	3.52	0.5	29	1.42	0.35	5.71	0.62
African American	MHDQT	152	2.97	1.29	6.84	0.011[2]	207	2.08	1.09	3.98	0.027	257	2.14	1.16	3.93	0.015
African American	LDQT	198	1.48	0.81	2.72	0.20	143	2.02	0.92	4.43	0.081	93	1.42	0.56	3.64	0.46
Model 2: Full																
Females	MHDQT	153	1.58	0.52	4.85	0.42	165	2.33	0.97	5.59	0.059	208	2.58	1.14	5.84	0.023
Females	LDQT	133	1.99	0.91	4.34	0.084	121	2.45	1.06	5.66	0.036	78	2.04	0.77	5.41	0.15
Males	MHDQT	128	2.11	0.77	5.81	0.147	233	1.42	0.89	2.26	0.28	274	1.43	0.79	2.59	0.24
Males	LDQT	190	0.71	0.35	1.44	0.34	85	0.62	0.19	2.06	0.44	44	0.55	0.06	4.75	0.59
White	MHDQT	129	1.46	0.34	6.33	0.61	191	1.25	0.58	2.67	0.57	225	1.22	0.52	2.90	0.56
White	LDQT	125	1.24	0.57	2.71	0.58	63	1.25	0.46	3.42	0.66	29	1.87	0.33	10.72	0.48
African American	MHDQT	152	3.13	1.28	7.64	0.012[2]	207	2.29	1.12	4.65	0.022	257	2.49	1.28	4.84	0.007[2]
African American	LDQT	198	1.56	0.81	2.99	0.18	143	2.10	0.89	4.99	0.092	93	1.46	0.52	4.08	0.47

Abbreviations: DII, Dietary Inflammatory Index; GDF15, growth/differentiation factor 15; GDF15H, high $\log_e$-transformed GDF15 (T3 vs. T1/T2); HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; HEI, Healthy Eating Index; HR, hazard ratio; LCL, lower 95% confidence limit; LDQT, low diet quality trajectory; ln, natural logarithm; MAR, mean adequacy ratio; MHDQT, medium or high diet quality trajectory; *N′* = number of observations in person–period format; SE, standard error; T = tertile; T_1 = first tertile; T_2 = second tertile; T_3 = third tertile; UCL, upper 95% confidence limit.

[1] Values are ln(HR) for main effects of GDF15H on frailty risk from Cox proportional hazards models adjusted for age, sex, race, and poverty status (Model 1) and additionally adjusted for education, current smoking, and drug use (Model 2). Models are stratified alternatively by sex and race. Within sex and racial groups, they were stratified alternatively by HEI-2010, DII, and MAR trajectory groups (HDQT vs. LDQT).

[2] $P < 0.05$ after familywise Bonferroni correction (type I error adjusted to 0.0125 for main effects).

[3] $P < 0.05$ after familywise Bonferroni correction for 2-way interaction between elevated GDF15 and LDQT (type I error adjusted to 0.0125) in a separate unstratified model (see Table 3).

relationship between GDF15 and diet quality. Low GDF15 was associated with better diet quality in older (mean age of 71.6 y) adults in the Seniors-ENRICA (Study on Nutrition and Cardiovascular Risk)-2 cohort in Spain [57]. In the Framingham Heart Study, GDF15 mediated the association of diet quality (measured using the Alternate HEI) with all-cause mortality and incident cardiovascular disease [58]. However, GDF15 was either not analyzed or no relationship was detected in validation studies [59]. Sex differences in the associations of diet quality or GDF15 with various health outcomes have rarely been studied. Therefore, larger studies are needed to examine the interplay between diet quality, GDF15, and sex in relation to frailty, cardiovascular disease, and mortality. There are several biological mechanisms that are thought to contribute to the sex–frailty paradox, where females have higher prevalence of frailty yet live longer than men [60]. These biological factors include genetic, hormonal, and immunological factors and the burden of chronic disease and disability [60]. Recent data from the HANDLS study also indicate sex-specific transcriptional differences between middle-aged frail females and males that were associated with biological processes such as cell cycle regulation, metabolism, and immune responses [61].

Strengths and limitations

The present study has several strengths. First, serum GDF15 was examined in the context of diet quality and frailty in a community-based population of middle-aged African American and White adults. Few studies have examined diet quality trajectories in a biracial cohort, using a data-driven method for classifying diet quality trajectories over time such as GBTM. In addition, unlike this study, frailty is often investigated among cohorts of older adults with ages >60 y at baseline with mainly European ancestry. Second, this study incorporated longitudinal multiple repeats of diet data from a follow-up period of 12 y. The diet data were gathered using 2 24-h recalls within each wave of data, and these were collected on separate days, which allows for the collection of data on both weekdays and weekend days [62]. At each visit, we implemented the AMPM, a well-established recall method that reduces measurement error in the collection of dietary data [63]. Third, in the present study, we also utilized 3 different dietary indices, allowing testing of interactions with GDF15 serum concentration in relation to frailty occurrence over time, using both micronutrient-based measures such as MAR and largely food-based measures such as HEI-2010 and DII. Comparison of these measures in terms of their trajectories over time was previously conducted on a larger sample of HANDLS in one study [64], while another recent study on a comparable sample as the first study examined their association with frailty incidence and trajectory [36]. Fourth, we used advanced statistical techniques, including GBTM, which allowed us to classify participants into categories based on diet quality and to use these categories to analyze the relationship between diet quality, frailty, and GDF15 serum concentration.

The strengths of our study should also be considered in light of several limitations. Although the AMPM is a validated recall method, dietary recalls are subject to underreporting of energy

intake and are not designed to capture habitual or long-term dietary intake, unlike other tools such as food frequency questionnaires [65]. This is particularly the case when outcomes such as frailty occur over a relatively long period of time. HANDLS is a biracial middle-aged cohort living in an urban setting, and the data here may not be generalizable to other populations with differing demographic and geographic characteristics. Specifically, this sample had a high proportion of smokers compared to the average US middle-aged population. This is also relevant considering that lower percentages of HANDLS participants fell into the high-quality diet index categories, indicating that overall, the diet quality in this cohort is low. Although we used BIC to select the number of subgroups for GBTM, this approach may not appropriately estimate the number of groups. Furthermore, event dates were reliant on examination date, specifically age at examination. Therefore, the exact age at which frail/-prefrail status started could not be determined accurately. Related to this latter limitation, in our present study we only used one specific measure of frailty, although others are available. To reduce measurement error, future studies should combine several types of metrics and conduct analyses using a structural equations modeling framework with latent variables. Moreover, several of our stratified analyses by sex and by race may have been underpowered, particularly those that further stratified by diet quality trajectory groups. Lastly, as in all observational studies, residual confounding is a limitation and here we were not able to also account for physical exercise as this was not analyzed in visit 1 of HANDLS. However, the role of GDF15 and exercise is complex and likely depends on the type, duration, and timing of release after exercise [66].

Conclusions

Interaction between GDF15 serum concentration and diet quality, particularly HEI-2010, in relation to incidence of frailty was detected in males. Specifically, elevated GDF15 was associated with increased risk of frailty in males, more so when diet quality was better. Further studies are needed to investigate and potentially replicate these sex-specific findings and to further study GDF15 and frailty and mediating factors between diet quality and other downstream health outcomes including all-cause and cause-specific mortality.

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Author contributions

The authors' responsibilities were as follows – conceptualization: MAB, NNH, MTF-K; plan of analysis: MAB, NNH, MTF-K, CAMV, MFG, ABZ; data acquisition: NNH, MTF-K, DF, MKE, ABZ; data management: MAB, ABZ; statistical analysis: MAB, MFG; literature search and review: MAB, NNH, MTF-K, CAMV, HAB; manuscript writing: MAB, NNH, MTF-K, CAMV, MFG, HAB, DF, MKE, ABZ; manuscript revision: MAB, NNH, MTF-K, CAMV, MFG, HAB, DF, MKE, ABZ; MAB: had full access to the data used in this manuscript; and all authors: read and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Data availability

The study protocol (09-AG-N248) received approval from the NIH National Institute on Environmental Health Sciences Institutional Review Board (IRB). Upon request, data can be made available to researchers with approved proposals after they have agreed to confidentiality as required by our IRB. Policies are available at https://handls.nih.gov. Data access requests can be sent to the principal investigators (PIs) or the study manager, Jennifer Norbeck, at norbeckje@mail.nih.gov. These data are owned by the NIH National Institute on Aging. The PIs have made the data restricted to the public for 2 main reasons: "(1) The study collects medical, psychological, cognitive, and psychosocial information on racial and poverty differences that could be misconstrued or willfully manipulated to promote racial discrimination; and (2) Although the sample is fairly large, there are sufficient identifiers that the PIs cannot guarantee absolute confidentiality for every participant as we have stated in acquiring our confidentiality certificate."

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2024.03.006.

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FIGURE LEGENDS

Figure 1. Participant flowchart: HANDLS 2004-2017

Abbreviations: GBTM = Group-based trajectory models; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; PH = Proportional hazards.

Figures 2. Group-based trajectory model findings for diet quality indices: HANDLS 2004-2017[1]

Abbreviations: DII = Dietary Inflammatory Index; HEI = Healthy Eating Index; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span ; MAR = Mean Adequacy Ratio.

[1] Diet quality trajectories are grouped as high, medium and low, as follows: Green=”High diet quality”; Red=”Medium diet quality”; Blue=”Low diet quality”. Percentages are means predicted probabilities from the GBTM model for each group and for each diet quality index.

Figure 3. Association between trajectories of diet quality indices, LnGDF15 tertiles and probability of remaining non-frail: Kaplan-Meier survival curves and scatterplot matrix, HANDLS 2004-2017[1,2]

Abbreviations: GDF15 = Plasma growth/differentiation factor 15; DII = Dietary Inflammatory Index; GBTM = Group-based trajectory models; HEI = Healthy Eating Index; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span ; MAR = Mean Adequacy Ratio.

[1] Diet quality trajectories are grouped as high, medium and low, as follows: Green=”High diet quality”; Red=”Medium diet quality”; Blue=”Low diet quality”.

[2] Scatterplot matrices are shown for descriptive purposes between baseline diet quality indices and LnGDF15.

Table 1. Study sample characteristics by sex and by race: HANDLS 2004-2017[1]

	Overall	Female	Male	White	African American	P^2_{sex}	P^2_{race}
	(X or % ± SE)	(X or % ± SE)	(X or % ± SE)	(X or % ± SE)	(X or % ± SE)		
	(N=945)	(N=505)	(N=440)	(N=408)	(N=537)		
X ±SE or %±SE							
GDF15 at v_1, pg/mL							
Log_e transformed, Ln	6.52±0.02	6.45±2.8	6.60±0.03	6.50±0.03	6.54±3.0	0.001	0.36
T_1: 4.43-6.17	31.3±1.5	34.7±2.1	27.5±2.1	30.9±2.0	31.7±2.0	0.005	0.83
T_2: 6.18-6.67	31.6±1.5	32.1±2.1	31.1±2.2	31.9±2.3	31.5±2.0	0.12	0.99
T_3: 6.67-9.33	37.0±1.6	33.3±2.1	41.4±2.3	37.3±2.4	36.9±2.1	Ref	Ref
Baseline socio-demographic, SES and health-related variables							
Sex, % male	46.6±1.6	0.0	100.0	47.3±2.5	46.0±2.2	__	0.69
Age at v_1, yrs.	49.4±0.3	49.4±0.4	49.5±0.4	49.7±0.5	49.2±0.4	0.88	0.41
African American, %	56.8±1.6	57.4±2.2	56.1±2.4	0.0	100.0	0.69	__
Poverty status, % <125% of the 2004 federal poverty guidelines	42.9±1.6	45.9±2.2	39.3±2.3	35.8±2.4	48.2±2.1	0.040	<0.001
Education, Completed, %							
<HS	6.6±0.8	4.8±1.0	8.7±1.3	9.8±1.5	4.2±0.9	0.032	<0.001
HS	59.0±1.6	59.1±2.2	58.9±2.4	50.9±2.5	65.1±2.1	Ref	Ref
>HS	34.4±1.5	36.1±2.2	32.5±2.2	39.3±2.4	30.7±2.0	0.47	<0.001
Baseline drug and tobacco use							
Any drug, current user, %	19.1±1.4	14.4±1.8	24.5±2.1	13.2±1.7	23.6±2.0	0.001	<0.001

Tobacco, current user, %	49.5±1.7	43.6±2.3	56.4±2.4	42.9±2.5	54.6±2.2	<0.001	<0.001
Frailty status at v_1	N=931	N=497	N=434	N=404	N=527		
Non-frail	51.0±1.6	42.9±2.2	60.4±2.3	52.7±2.5	49.7±2.2	Ref	Ref
Pre-frail	36.1±1.6	40.8±2.2	30.6±2.2	31.7±2.3	39.5±2.1	<0.001	0.055
Frail	12.9±1.1	16.3±1.7	9.0±1.4	15.6±1.8	10.8±1.4	<0.001	0.13
Frailty status at v_2	N=552	N=303	N=249	N=250	N=302		
Non-frail	46.9±2.1	40.3±2.8	55.0±3.1	45.6±3.2	48.0±2.9	Ref	Ref
Pre-frail	37.7±2.1	38.6±2.8	36.5±3.1	37.6±3.1	37.7±2.8	0.050	0.80
Frail	15.4±1.5	21.1±2.3	8.4±1.8	16.8±2.4	14.2±2.0	<0.001	0.39
Frailty status at v_3	N=564	N=326	N=238	N=241	N=323		
Non-frail	50.2±2.1	45.7±2.8	56.3±3.2	47.7±3.2	52.0±2.8	Ref	Ref
Pre-frail	33.9±2.0	35.0±2.6	32.4±3.0	36.0±3.1	32.2±2.6	0.13	0.29
Frail	16.0±1.5	19.3±2.2	11.3±2.0	16.2±2.4	15.8±2.0	0.004	0.65
HEI-2010 diet quality trajectory							
Low	61.9±1.6	57.2±2.2	67.3±2.2	61.3±2.4	62.4±2.1	Ref	Ref
Medium	33.7±1.5	37.2±2.2	29.5±2.2	32.4±2.3	34.6±2.1	0.005	0.72
High	4.4±0.7	5.5±1.0	3.2±0.8	6.4±1.2	3.0±0.7	0.034	0.018
DII diet quality trajectory							
Low	43.6±1.6	49.7±2.2	36.6±2.2	39.2±2.4	46.9±2.2	<0.001	0.22
Medium	47.5±1.6	43.6±2.2	52.0±2.4	47.3±2.5	47.7±2.2	Ref	Ref
High	8.8±0.9	6.7±1.1	11.4±1.5	13.5±1.6	5.4±1.0	0.15	<0.001
MAR diet quality trajectory							
Low	24.3±1.4	31.9±2.1	15.7±1.7	19.9±2.0	27.7±1.9	<0.001	0.087
Medium	46.6±1.6	44.8±2.2	48.6±2.4	45.3±2.5	47.5±2.2	Ref	Ref

High	29.1±1.5	23.4±1.9	35.7±2.3	34.8±2.4	24.8±1.9	0.028	0.012

Abbreviations: DII=Dietary Inflammatory Index; GBTM = Group-based trajectory models; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; HEI-2010=Healthy Eating Index, 2010 revision; Ln=Natural Logarithm; MAR=Mean Adequacy Ratio; N=Number of participants; SE = Standard error; T=Tertile; T_1=First tertile; T_2=Second tertile; T_3=Third tertile.

[1]Values are means (X) ±SE for continuous variables and % for categorical variables. See **Figure 1** for participant flowchart. 1 SD of LnGDF15 is equivalent to a value of 0.669.

[2]P for null hypothesis that β=0 from models that included sex or race as the only predictors. Models were OLS linear regression models for continuous variables and multinomial logit models for categorical variables, applied to multiple imputed data.

Table 2. LnGDF15 tertiles, diet quality trajectory groups and frailty incidence: Cox PH models: HANDLS 2004-2017[1]

	Overall		Female		Male		White		African American	
	β ± SE	P	β ± SE	P	β ± SE	P	β ± SE	P	β ± SE	P
	(N'=604, N=400)		(N'=286, N=184)		(N'=318, N=216)		(N'=254, N=174)		(N'=350, N=226)	
HEI-2010										
Model 1										
GBTM group 2 vs. group 1: Medium vs. Low	-0.202±0.174	0.25	+0.021±0.240	0.93	-0.359±0.263	0.17	-0.526±0.286	0.066	+0.134±0.225	0.55
GBTM group 3 vs. group 1: High vs. Low	-1.495±0.474	0.002[2]	-1.625±0.625	0.009[2]	-0.731±0.743	0.33	-1.444±0.576	0.012	-1.639±1.012	0.11
LnGDF15										
T_2 vs. T_1	-0.012±0.199	0.95	-0.409±0.284	0.15	+0.470±0.305	0.12	+0.271±0.297	0.36	-0.381±0.273	0.16
T_3 vs. T_1	0.439±0.231	0.058	+0.527±0.330	0.11	+0.637±0.352	0.070	+0.424±0.368	0.25	+0.460±0.296	0.12
Model 2										
GBTM group 2 vs. group 1: Medium vs. Low	-0.175±0.180	0.33	-0.059±0.255	0.82	-0.249±0.274	0.37	-0.419±0.308	0.17	+0.083±0.231	0.72
GBTM group 3 vs. group 1: High vs. Low	-1.460±0.490	0.003[2]	-1.914±0.662	0.004[2]	-0.557±0.756	0.46	-1.247±0.639	0.051	-1.672±1.02	0.10
LnGDF15										
T_2 vs. T_1	-0.015±0.209	0.95	-0.342±0.304	0.26	+0.346±0.318	0.28	+0.203±0.315	0.52	-0.405±0.284	0.15
T_3 vs. T_1	+0.456±0.247	0.064	+0.656±0.347	0.059	+0.510±0.382	0.18	+0.400±0.393	0.310	+0.489±0.318	0.12
DII										
Model 1										
GBTM group 2 vs. group 1: Medium vs. Low	-0.244±0.168	0.15	-0.241±0.225	0.29	-0.217±0.255	0.39	-0.136±0.260	0.60	-0.248±0.222	0.26

GBTM group 3 vs. group 1: High vs. Low	-1.423±0.372	<0.001[2]	-1.661±0.644	0.010[2]	-1.117±0.469	0.017	-1.282±0.466	0.006[2]	-1.575±0.739	0.033
LnGDF15										
T_2 vs. T_1	-0.016±0.199	0.94	-0.438±0.284	0.12	+0.478±0.301	0.39	+0.288±0.298	0.34	-0.382±0.274	0.16
T_3 vs. T_1	0.468±0.230	0.041	+0.482±0.322	0.13	+0.659±0.348	0.058	+0.528±0.357	0.14	+0.460±0.295	0.12
Model 2										
GBTM group 2 vs. group 1: Medium vs. Low	-0.222±0.171	0.19	-0.262±0.231	0.26	-0.165±0.261	0.53	-0.108±0.268	0.69	-0.246±0.224	0.27
GBTM group 3 vs. group 1: High vs. Low	-1.385±0.384	<0.001[2]	-1.920±0.675	0.004[2]	-0.986±0.483	0.041	-1.122±0.505	0.026	-1.665±0.742	0.025
LnGDF15										
T_2 vs. T_1	-0.029±0.208	0.89	-0.417±0.299	0.16	+0.350±0.316	0.27	+0.221±0.314	0.48	-0.396±0.285	0.16
T_3 vs. T_1	+0.470±0.246	0.056	+0.602±0.343	0.080	+0.520±0.381	0.17	+0.479±0.388	0.22	+0.490±0.318	0.12
MAR										
Model 1										
GBTM group 2 vs. group 1: Medium vs. Low	-0.196±0.196	0.32	-0.203±0.253	0.42	-0.241±0.326	0.46	+0.251±0.337	0.46	-0.142±0.243	0.56
GBTM group 3 vs. group 1: High vs. Low	-0.600±0.230	0.009[2]	-0.682±0.332	0.040	-0.546±0.350	0.12	-0.578±0.367	0.12	-0.576±0.322	0.074
LnGDF15										
T_2 vs. T_1	+0.025±0.200	0.90	-0.440±0.287	0.13	+0.531±0.300	0.076	+0.383±0.298	0.20	-0.399±0.276	0.15
T_3 vs. T_1	+0.539±0.229	0.018	+0.529±0.319	0.098	+0.750±0.346	0.030	*+0.645±0.360*	*0.073*	+0.478±0.294	0.10
Model 2										
GBTM group 2 vs. group 1: Medium vs. Low	-0.220±0.197	0.27	-0.232±0.261	0.38	-0.224±0.331	0.50	-0.170±0.341	0.62	-0.156±0.247	0.53
GBTM group 3 vs. group 1: High vs. Low	-0.586±0.231	0.011[2]	-0.726±0.340	0.033	-0.491±0.354	0.17	-0.408±0.376	0.28	-0.653±0.328	0.047
LnGDF15										
T_2 vs. T_1	-0.022±0.208	0.92	-0.422±0.302	0.16	+0.368±0.314	0.24	+0.239±0.316	0.45	-0.427±0.286	0.14

T_3 vs. T_1	+0.482±0.245	0.049	+0.553±0.338	0.10	+0.543±0.383	0.16	0.512±0.390	0.19	+0.476±0.318	0.13

Abbreviations: DII=Dietary Inflammatory Index; GBTM = Group-based trajectory models; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; HEI-2010=Healthy Eating Index, 2010 revision; HR=Hazard Ratio; Ln=Natural Logarithm; MAR=Mean Adequacy Ratio; N=Number of participants; N'=Number of observations in person-period format; PH = Proportional hazards; SE = Standard error; T=Tertile; T_1=First tertile; T_2=Second tertile; T_3=Third tertile.

[1]Values are Ln(HR) for main effects of diet quality trajectories comparing medium to low and high to low; and main effects of LnGDF15 comparing T_3 to T_1 and T_2 to T_1. See ranges of LnGDF15 tertiles in Table 1.

[2] P<0.05 after familywise Bonferroni correction (type I error adjusted to 0.0125 for main effects and 0.025 for 2-way interaction terms).

Table 3. Interactions between GDF15H [Elevated LnGDF15 (T_3 vs. T_1/T_2)] and LDQT ["Low" diet quality trajectories (vs. Medium/high)] in relation to frailty incidence: Cox PH models, HANDLS 2004-2017[1]

	Overall		Female		Male		White		African American	
	β ± SE	P	β ± SE	P	β ± SE	P	β ± SE	P	β ± SE	P
	(N'=604, N=400)		(N'=286, N=184)		(N'=318, N=216)		(N'=254, N=174)		(N'=350, N=226)	
HEI-2010										
Model 1										
LDQT	+0.490±0.197	0.013	+0.145±0.270	0.59	+0.781±0.310	0.012[2]	+0.815±0.307	0.008[2]	+0.081±0.260	0.76
GDF15H	+0.824±0.326	0.011[2]	+0.456±0.545	0.40	+1.148±0.432	0.002[2]	+0.680±0.567	0.23	+0.899±0.402	0.025
LDQT× GDF15H	-0.519±0.378	0.17	+0.418±0.620	0.50	-1.173±0.507	0.021[2]	-0.590±0.629	0.35	-0.301±0.482	0.53
Model 2										
LDQT	+0.424±0.208	0.042	+0.211±0.292	0.47	+0.621±0.326	0.057	+0.577±0.363	0.11	+0.120±0.264	0.65
GDF15H	+0.777±0.335	0.020	+0.544±0.557	0.33	+1.027±0.441	0.020	+0.472±0.597	0.43	+0.914±0.412	0.027
LDQT× GDF15H	-0.458±0.383	0.23	+0.316±0.632	0.62	-1.148±0.529	0.030	-0.324±0.672	0.63	-0.253±0.486	0.60
DII										
Model 1										
LDQT	+0.479±0.199	0.016	+0.405±0.267	0.13	+0.579±0.310	0.063	+0.425±0.323	0.19	+0.407±0.261	0.12
GDF15H	+0.643±0.235	0.006[2]	+0.904±0.395	0.022	+0.529±0.297	0.075	+0.496±0.353	0.16	+0.790±0.317	0.013
LDQT× GDF15H	-0.302±0.345	0.38	-0.184±0.507	0.72	-0.596±0.505	0.24	-0.303±0.519	0.56	-0.239±0.469	0.61
Model 2										

LDQT	+0.433±0.203	0.033	+0.430±0.275	0.12	+0.478±0.319	0.13	+0.256±0.339	0.45	*0.450±0.263*	*0.088*
GDF15H	+0.619±0.243	0.011[2]	+0.967±0.414	0.020	+0.405±0.311	0.19	+0.386±0.366	0.29	+0.872±0.332	0.009
LDQT× GDF15H	-0.316±0.346	0.36	-0.264±0.519	0.61	-0.600±0.512	0.24	-0.188±0.526	0.72	-0.302±0.476	0.53
MAR										
Model 1										
LDQT	+0.375±0.221	0.090	+0.381±0.283	0.18	+0.512±0.364	0.16	0.385±0.413	0.35	+0.346±0.267	0.20
GDF15H	+0.577±0.213	0.007[2]	+0.846±0.346	0.015	+0.457±0.278	0.10	0.400±0.319	0.21	+0.792±0.292	0.007[2]
LDQT× GDF15H	-0.138±0.406	0.734	-0.105±0.527	0.84	-0.511±0.715	0.48	-0.022±0.646	0.97	-0.288±0.542	0.60
Model 2										
LDQT	+0.368±0.222	0.097	+0.400±0.291	0.17	+0.505±0.370	0.17	+0.270±0.422	0.52	+0.348±0.269	0.20
GDF15H	+0.522±0.222	0.019	+0.400±0.378	0.030	+0.332±0.294	0.26	+0.334±0.335	0.32	+0.818±0.310	0.008[2]
LDQT× GDF15H	-0.083±0.412	0.84	-0.085±0.551	0.88	-0.621±0.733	0.40	-0.068±0.675	0.92	-0.210±0.554	0.71

Abbreviations: DII = Dietary Inflammatory Index; GDF15 = Plasma growth/differentiation factor 15; GDF15H= High Log_e-transformed GDF15; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; HEI = Healthy Eating Index; HR = Hazard ratio; LDQT = low diet quality trajectories; Ln=Natural logarithm; MAR = Mean Adequacy Ratio; N=Number of participants; N'=Number of observations in person-period format; SE = Standard error; T=Tertile; T_1=First tertile; T_2=Second tertile; T_3=Third tertile.

[1] Values are Ln(HR) for main effects of low diet quality trajectories (LDQT), High LnGDF15 (GDF15H) and 2-way interaction between the two variables.

[2] P<0.05 after familywise Bonferroni correction (type I error adjusted to 0.0125 for main effects and 0.025 for 2-way interaction terms).

Table 4. GDF15H **[**Elevated LnGDF15 (T_3 vs. T_1/T_2)] in relation to frailty incidence across diet quality trajectory groups ["Low" diet quality trajectories, or LDQT vs. Medium/high or MHDQT]: Cox PH models: HANDLS 2004-2017[1]

		HEI-2010					DII					MAR				
		N'	HR	LCL	UCL	P	N'	HR	LCL	UCL	P	N'	HR	LCL	UCL	P
Model 1: Reduced																
Females	MHDQT	153	1.57	0.53	4.66	0.42	165	2.10	0.92	4.79	0.077	208	2.25	1.08	4.71	0.031
Females	LDQT	133	1.87	0.91	3.82	0.086	121	2.23	1.04	4.80	0.039	78	1.91	0.81	4.51	0.14
Males	MHDQT	128	2.69	1.10	6.60	0.031[3]	233	1.65	0.90	3.03	0.1	274	1.57	0.90	2.75	0.11
Males	LDQT	190	0.94	0.49	1.79	0.86	85	0.79	0.30	2.12	0.65	44	0.43	0.08	2.38	0.33
White	MHDQT	129	1.80	0.62	5.18	0.32	191	1.49	0.72	3.06	0.28	225	1.29	0.68	2.45	0.44
White	LDQT	125	1.20	0.59	2.46	0.61	63	1.38	0.54	3.52	0.5	29	1.42	0.35	5.71	0.62
African American	MHDQT	152	2.97	1.29	6.84	0.011[2]	207	2.08	1.09	3.98	0.027	257	2.14	1.16	3.93	0.015
African American	LDQT	198	1.48	0.81	2.72	0.20	143	2.02	0.92	4.43	0.081	93	1.42	0.56	3.64	0.46
Model 2: Full																
Females	MHDQT	153	1.58	0.52	4.85	0.42	165	2.33	0.97	5.59	0.059	208	2.58	1.14	5.84	0.023
Females	LDQT	133	1.99	0.91	4.34	0.084	121	2.45	1.06	5.66	0.036	78	2.04	0.77	5.41	0.15
Males	MHDQT	128	2.11	0.77	5.81	0.147	233	1.42	0.89	2.26	0.28	274	1.43	0.79	2.59	0.24
Males	LDQT	190	0.71	0.35	1.44	0.34	85	0.62	0.19	2.06	0.44	44	0.55	0.06	4.75	0.59
White	MHDQT	129	1.46	0.34	6.33	0.61	191	1.25	0.58	2.67	0.57	225	1.22	0.52	2.90	0.56
White	LDQT	125	1.24	0.57	2.71	0.58	63	1.25	0.46	3.42	0.66	29	1.87	0.33	10.72	0.48
African American	MHDQT	152	3.13	1.28	7.64	0.012[2]	207	2.29	1.12	4.65	0.022	257	2.49	1.28	4.84	0.007[2]
African American	LDQT	198	1.56	0.81	2.99	0.18	143	2.10	0.89	4.99	0.092	93	1.46	0.52	4.08	0.47

Abbreviations: DII = Dietary Inflammatory Index; GDF15 = Plasma growth/differentiation factor 15; GDF15H= High Log_e-transformed GDF15; HANDLS = Healthy Aging in Neighborhoods of Diversity across the Life Span; HEI = Healthy Eating Index; HR = Hazard ratio; LCL=Lower 95% confidence limit; LDQT =

low diet quality trajectories; Ln=Natural logarithm; MAR = Mean Adequacy Ratio; MHDQT= Medium or High Diet Quality Trajectory; N=Number of participants; N'=Number of observations in person-period format; SE = Standard error; UCL=Upper 95% confidence limit; T=Tertile; T_1=First tertile; T_2=Second tertile; T_3=Third tertile.

[1] Values are Ln(HR) for main effects of High LnGDF15 (GDF15H) on frailty risk from Cox proportional hazards models adjusted for age, sex, race and poverty status (Model 1) and additionally adjusted for education, current smoking and drug use (Model 2). Models are stratified alternatively by sex and race. Within sex and racial groups, they were stratified alternatively by HEI-2010, DII and MAR trajectory groups (HDQT vs. LDQT).

[2] P<0.05 after familywise Bonferroni correction (type I error adjusted to 0.0125 for main effects).

[3] P<0.05 after familywise Bonferroni correction for 2-way interaction between elevated GDF15 and lower diet quality trajectory (type I error adjusted to 0.0125) in a separate unstratified model (See **Table 3**).

FIGURE 1.

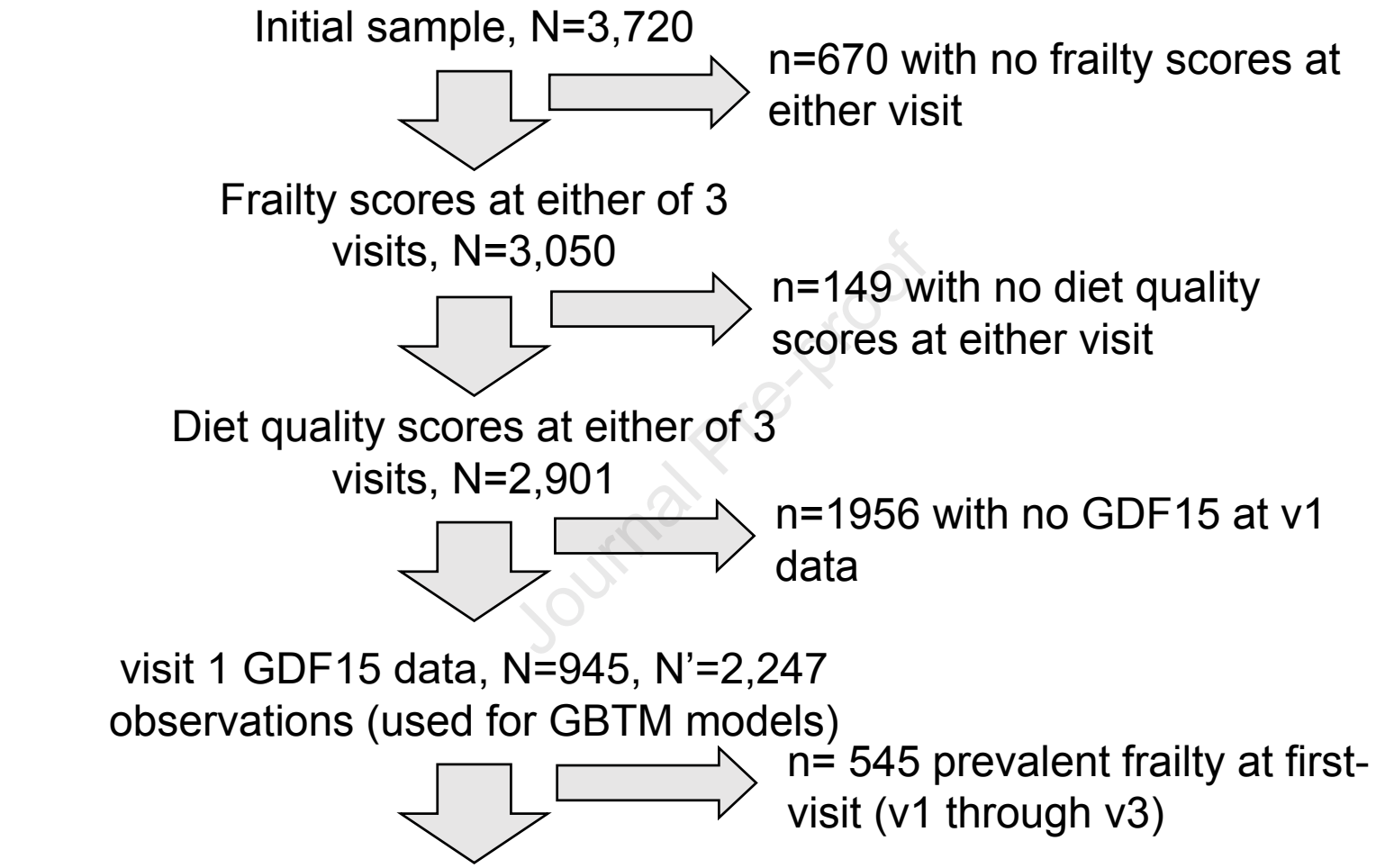


Figure 2

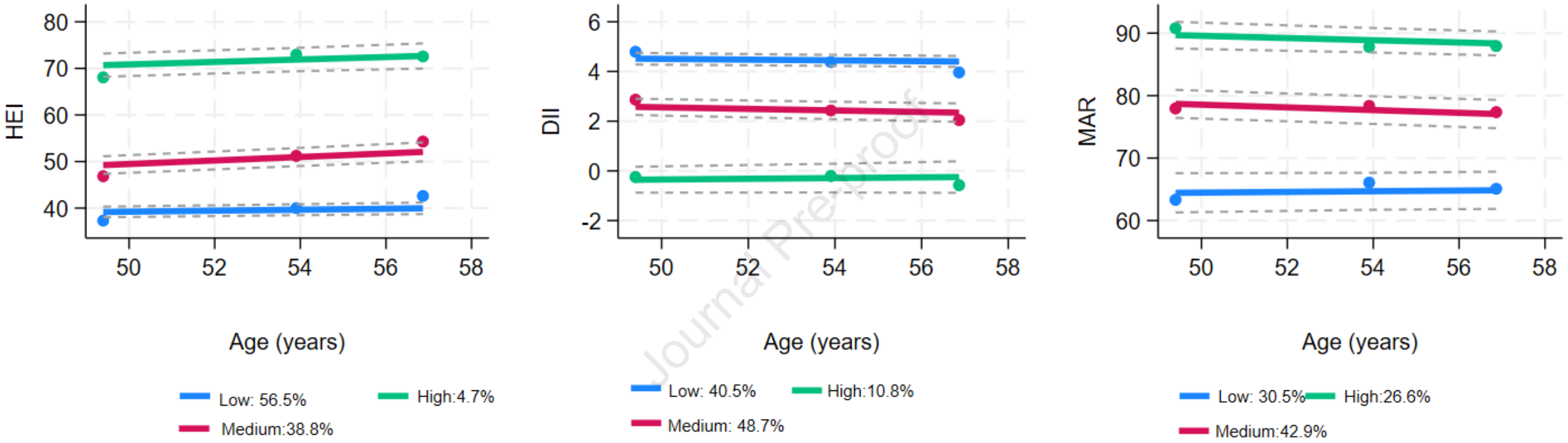
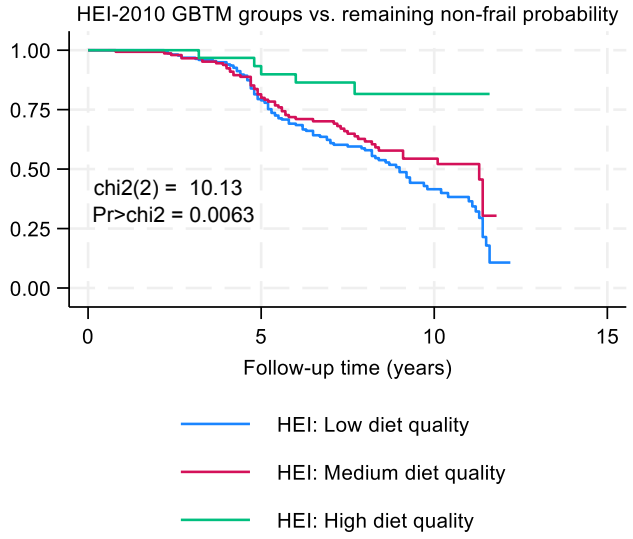
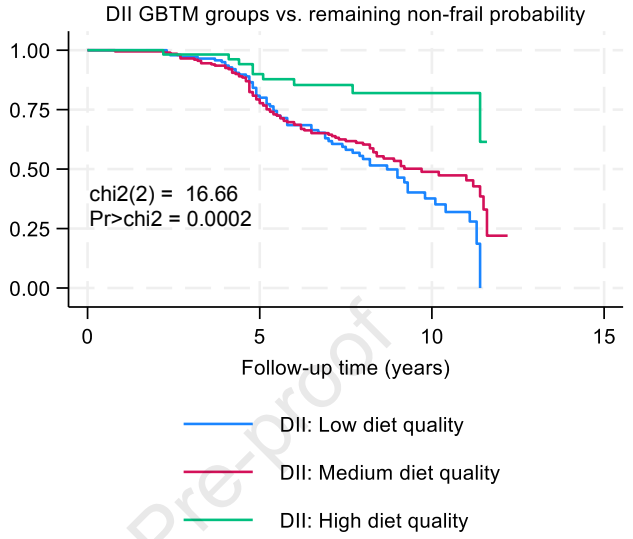
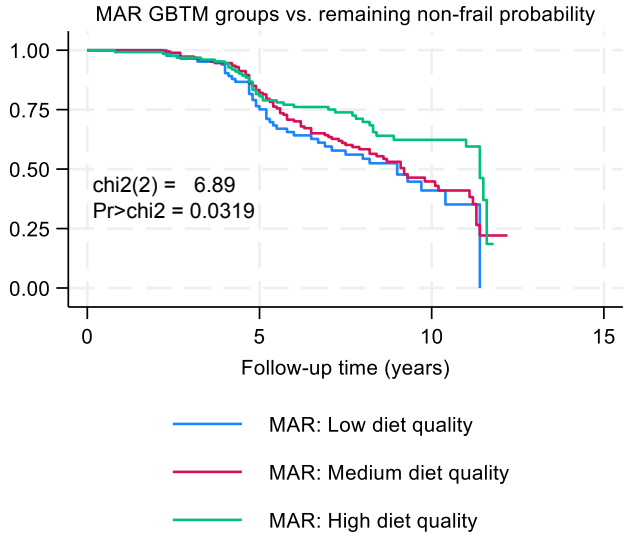
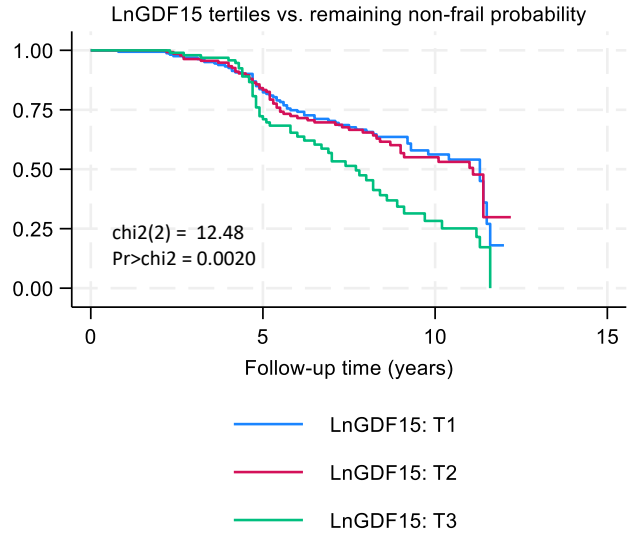


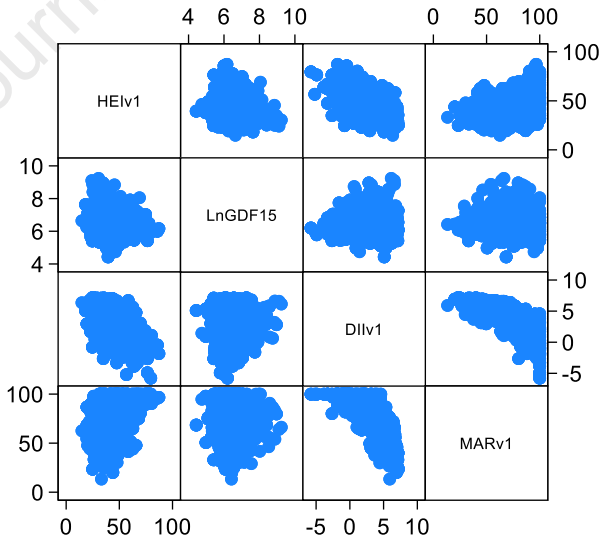
Figure 3.











Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

ONLINE SUPPLEMENTARY MATERIALS

Growth Differentiation Factor 15 and diet quality trajectory interact to determine frailty among middle-aged urban adults

Beydoun M. A. et al

Supplementary results 1: Group-based trajectory models results

Diet quality trajectory was recoded to reflect low, medium and high diet quality based on the trajplot and the mean diet quality indices at each wave per group:

1=Low diet quality, 2=Medium diet quality, 3=High diet quality.

```
capture drop R_traj_Group_DIETHEIrec
gen R_traj_Group_DIETHEIrec=.
replace R_traj_Group_DIETHEIrec=1 if R_traj_Group_DIETHEI==2
replace R_traj_Group_DIETHEIrec=2 if R_traj_Group_DIETHEI==1
replace R_traj_Group_DIETHEIrec=3 if R_traj_Group_DIETHEI==3
```

```
bysort  R_traj_Group_DIETDII: su DIETDII
```

```
capture drop R_traj_Group_DIETDIIrec
gen R_traj_Group_DIETDIIrec=.
replace R_traj_Group_DIETDIIrec=1 if R_traj_Group_DIETDII==2
replace R_traj_Group_DIETDIIrec=2 if R_traj_Group_DIETDII==3
replace R_traj_Group_DIETDIIrec=3 if R_traj_Group_DIETDII==1
```

```
capture drop R_traj_Group_DIETMARrec
gen R_traj_Group_DIETMARrec=.
replace R_traj_Group_DIETMARrec=1 if R_traj_Group_DIETMAR==1
replace R_traj_Group_DIETMARrec=2 if R_traj_Group_DIETMAR==3
replace R_traj_Group_DIETMARrec=3 if R_traj_Group_DIETMAR==2
```

1) **HEI-2010:**

Maximum Likelihood Estimates

Model: Censored Normal (cnorm)

Group	Parameter	Estimate	Standard Error	T for H0: Parameter=0	Prob > T
1	Intercept	30.63197	2.59848	11.788	0.0000
	Linear	0.37694	0.04930	7.646	0.0000
2	Intercept	33.97758	1.95047	17.420	0.0000
	Linear	0.10535	0.03735	2.820	0.0048
3	Intercept	57.64495	5.62363	10.250	0.0000
	Linear	0.26422	0.10604	2.492	0.0128
1	Sigma	9.72969	0.35365	27.512	0.0000
2	Sigma	8.53290	0.30337	28.127	0.0000
3	Sigma	8.81995	0.77652	11.358	0.0000
Group membership					
1	(%)	38.84696	5.68972	6.828	0.0000
2	(%)	56.49180	5.79782	9.744	0.0000
3	(%)	4.66125	0.88014	5.296	0.0000

BIC= -7561.51 (N=1972) BIC= -7557.46 (N=945) AIC= -7530.78 ll= -7519.78

Parameter estimates for adding risk factors

30.63197, 0.37694, 33.97758, 0.10535, 57.64495, 0.26422,

9.72969, 8.53290, 8.81995, 0.37447, -2.12035

Parameter estimates

30.63197, 0.37694, 33.97758, 0.10535, 57.64495, 0.26422,
9.72969, 8.53290, 8.81995, 38.84696, 56.49180, 4.66125

Entropy = 0.613

2) DII:

Maximum Likelihood Estimates

Model: Censored Normal (cnorm)

Group	Parameter	Estimate	Standard Error	T for H0: Parameter=0	Prob > T
1	Intercept	-1.05413	0.92146	-1.144	0.2528
	Linear	0.01417	0.01890	0.750	0.4536
2	Intercept	5.26408	0.37396	14.076	0.0000
	Linear	-0.01513	0.00641	-2.359	0.0184
3	Intercept	4.11504	0.43909	9.372	0.0000
	Linear	-0.03116	0.00884	-3.525	0.0004
1	Sigma	1.89580	0.12081	15.693	0.0000
2	Sigma	1.30491	0.05936	21.981	0.0000
3	Sigma	1.72289	0.05314	32.420	0.0000

Group membership

1	(%)	10.83432	2.32492	4.660	0.0000
2	(%)	40.46856	5.14775	7.861	0.0000
3	(%)	48.69712	4.65979	10.451	0.0000

BIC= -4178.60 (N=1972) BIC= -4174.56 (N=945) AIC= -4147.88 ll= -4136.88

Parameter estimates for adding risk factors

-1.05413, 0.01417, 5.26408, -0.01513, 4.11504, -0.03116,
1.89580, 1.30491, 1.72289, 1.31781, 1.50290

Parameter estimates

-1.05413, 0.01417, 5.26408, -0.01513, 4.11504, -0.03116,
1.89580, 1.30491, 1.72289, 10.83432, 40.46856, 48.69712

Entropy = 0.569

3) MAR

Maximum Likelihood Estimates

Model: Censored Normal (cnorm)

Group	Parameter	Estimate	Standard Error	T for H0: Parameter=0	Prob > T
1	Intercept	61.83473	4.86910	12.699	0.0000
	Linear	0.05495	0.08538	0.644	0.5200
2	Intercept	99.28138	2.79827	35.480	0.0000
	Linear	-0.18890	0.04813	-3.924	0.0001
3	Intercept	89.59070	3.04073	29.464	0.0000
	Linear	-0.21981	0.05618	-3.913	0.0001
1	Sigma	16.76332	0.61420	27.293	0.0000
2	Sigma	7.25198	0.40850	17.753	0.0000
3	Sigma	9.67914	0.54210	17.855	0.0000
Group membership					
1	(%)	30.53704	4.08427	7.477	0.0000
2	(%)	26.61103	4.14635	6.418	0.0000
3	(%)	42.85194	4.74687	9.027	0.0000

BIC= -7827.03 (N=1972) BIC= -7822.98 (N=945) AIC= -7796.30 ll= -7785.30

Parameter estimates for adding risk factors

61.83473, 0.05495, 99.28138, -0.18890, 89.59070, -0.21981,
16.76332, 7.25198, 9.67914, -0.13761, 0.33881

Parameter estimates

61.83473, 0.05495, 99.28138, -0.18890, 89.59070, -0.21981,
16.76332, 7.25198, 9.67914, 30.53704, 26.61103, 42.85194

Entropy = 0.473