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# Re-analysis of the DISC Study: Advanced Statistical Approaches to Understanding Dietary Interventions in Pediatric Cardiovascular Health

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## SUMMARY

Background: The Dietary Intervention Study in Children (DISC) showed that a cholesterol-lowering dietary intervention can improve pediatric cardiovascular risk factors. Building on advances in longitudinal modeling, we re-analyzed DISC data to (1) reassess intervention effects using linear and spline mixed-effects models, (2) evaluate treatment effects within key subgroups, and (3) examine the impact of compliance on percent calories from fats.
Methods: We conducted a secondary analysis of the randomized DISC trial, comparing a dietary intervention group with a usual care group. Linear mixed-effects and B-spline mixed-effects models characterized trajectories of LDL-cholesterol and nutrient intake over time. We evaluated subgroup differences by sex and parental education and assessed compliance using session attendance and adherence to dietary goals for saturated fat, cholesterol, and total fat.
Results: Compared with usual care, the intervention group demonstrated a significantly steeper decline in LDL-cholesterol over time (treatment-by-time interaction $p = 0.027$), with the largest reduction observed during the first 12 months. Higher attendance at intervention sessions was associated with lower average percentage of calories from total fat ($\beta = -2.24$, SE 0.37, $p < 0.0001$) and saturated fat intake ($\beta = -1.07$, SE 0.18, $p < 0.0001$). Parental attendance was strongly associated with lower LDL-cholesterol levels ($\beta = -13.97$ mg/dL, SE 4.18, $p < 0.0001$). The intervention group had significantly higher proportions of participants meeting dietary goals for total fat, saturated fat, and cholesterol at 12 and 36 months (all $p < 0.001$).
Conclusion: This reanalysis indicates that a family-based dietary intervention initiated in childhood can produce meaningful reductions in LDL-cholesterol and sustained improvements in dietary fat intake. The findings highlight the importance of adherence, parental involvement, and targeted support for specific subgroups in promoting long-term cardiovascular health in pediatric populations.

*Keywords: Dietary intervention, pediatric cardiovascular health, linear mixed-effects models, spline models, adherence*

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## INTRODUCTION

This paper presents a comprehensive reanalysis of the long-term efficacy and safety of cholesterol-lowering dietary intervention in children, originally explored in the Dietary Intervention Study in Children (DISC; NCT00000459). The DISC study involved 663 children aged 8 to 10 years with elevated low-density cholesterol (LDL-C), randomized into either a dietary intervention group or a usual care group. Over an average follow-up of 7.4 years, the intervention promoted adherence to a diet with specified limits on total fat, saturated fat, polyunsaturated fat, and cholesterol intake.

The initial findings from DISC indicated significant reductions in LDL-C levels at 1 year, 3 years, and the final visit in the intervention group, with no adverse effects on growth or nutritional status, confirming the safety of the dietary modifications. Building on the original findings, the present study re-examines the DISC data using contemporary longitudinal modeling techniques to better characterize individual trajectories and time-varying intervention effects [1].

Supporting this research, a substantial body of evidence underscores the importance of intervening early in the life course to shape cardiometabolic risk. In 1992, the Expert Panel on Blood LDL-C Levels in Children and Adolescents emphasized that dietary modification beginning in childhood has the potential to reduce future cardiovascular risk, providing an early policy and clinical framework for pediatric lipid management [2]. Subsequent school-based trials have demonstrated that multicomponent programs targeting both diet and physical activity can improve dietary behaviors, physical fitness, and weight-related outcomes in children, reinforcing the value of integrating health promotion within everyday settings such as schools [3-5]. The Bright Bodies trial, for example, showed that a structured family- and behavior-based weight-management program could effectively address pediatric obesity, highlighting the need for comprehensive approaches that extend beyond isolated dietary advice [4].

Longitudinal work has also shown that dietary patterns and blood lipids evolve markedly across childhood, with school age emerging as a critical turning point for the establishment of eating habits [6]. Studies leveraging repeated measures have begun to characterize how trajectories of diet and lipid profiles relate over time. For instance, a 3-year cohort study of children aged 3–6 years found that higher consumption of ultra-processed foods was associated with persistently higher total LDL-C at both 3 and 6 years, based on linear regression models of repeated lipid measures [7]. Complementing these findings, a 2021 review concluded that early modification of dietary fat and LDL-C remains a key strategy for promoting cardiovascular health [8], while recent analyses of cumulative LDL-C exposure indicate that prolonged elevated LDL-C from childhood into adulthood is strongly linked with higher cardiovascular disease risk, and that relying solely on family-history–based selective screening is insufficient to detect many at-risk children [9].

The primary objective of this study was to reassess the long-term effects of the DISC dietary intervention using advanced longitudinal modeling approaches, including linear mixed-effects and spline-based models. Specifically, we aimed to (1) characterize time-varying intervention effects on LDL-C and dietary intake, (2) evaluate heterogeneity of treatment effects across key subgroups, and (3) examine the role of adherence and parental involvement in modifying intervention outcomes.

## MATERIALS AND METHODS

### Study Design

The DISC was a multicenter, randomized clinical trial that evaluated the effects of a LDL-C-lowering dietary intervention on pediatric cardiovascular risk. Children were randomized to a dietary intervention group or a usual care group and followed prospectively with repeated standardized measurements over an average of 7.4 years. The original trial protocol, operational procedures, and primary outcomes have been published in detail [1]. The present study preserves the original randomized allocation and data collection scheme and focuses on a longitudinal re-analysis using modern mixed-effects and spline-based models.

Study Population

DISC enrolled 663 children aged 8–10 years with elevated LDL-C, defined as fasting LDL-C between the 80th and 98th percentiles for age and sex based on Lipid Research Clinics reference data (mean baseline LDL-C ~130.5 mg/dL), as per the original trial eligibility criteria [10]. Participants were recruited from multiple clinical centers and randomized to receive either the DISC dietary intervention or usual care. The dietary intervention promoted adherence to a diet providing 28% of energy from total fat, less than 8% from saturated fat, up to 9% from polyunsaturated fat, and less than 75 mg/1000 kcal of cholesterol per day, while monitoring caloric adequacy to support normal growth [1]. Intervention strategies were grounded in social learning theory and social action theory, incorporating structured group sessions led by nutritionists and behaviorists and individual counseling visits, with later sessions transitioning to a motivational interviewing approach as participants entered adolescence [1]. Parents or guardians of children in the usual care group were informed of their child's elevated LDL-C and provided publicly available heart-healthy eating materials only [1]. For the current secondary analysis, all 663 randomized participants were included, and analyses were conducted under the original intention-to-treat framework.

## Statistical Analysis

The primary outcome of interest was LDL-C. Key dietary outcomes included average total calorie intake (AVE1), percentage of calories from total fat (AVE3), saturated fat (AVE7), polyunsaturated fat (AVE9), and cholesterol per 1000 kcal (AVE6). Covariates incorporated into the models included sex, treatment group, visit number, clinic, body mass index (BMI), Tanner stage, and components of the Keys Formula for dietary impact on LDL-C [11-13]. Additional analyses examined adherence-related measures, including training session attendance and adherence to dietary goals for AVE7, LDL-C, and AVE3. To evaluate the effects of the intervention over time, we used linear mixed-effects models (LMMs) incorporating fixed and random effects to account for intra-individual variability. The following covariates were all included as fixed effects: sex, treatment group, visit number, clinic, BMI, Tanner stage, and components of the Keys Formula for dietary impact on LDL-C. Two primary model structures were compared: one including an interaction between treatment and time (visit number), and another assuming consistent treatment effects across time points [11]. Model selection was guided by the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and likelihood ratio tests [12]. To assess potential non-linear trends in dietary outcomes, spline mixed effect models, using natural and B-splines, were also evaluated, with the final spline structure selected based on AIC [13]. These models allowed flexible estimation of outcome trajectories and tested for treatment-time interactions [14, 15]. All models were fitted using maximum likelihood estimation, which incorporates all available observations from each participant regardless of follow-up completeness, minimizing the potential for attrition bias under the missing-at-random assumption. Additional analyses assessed (1) the impact of compliance to the DISC diet within the intervention group, and (2) treatment effects across various subgroups, including those defined by training session attendance. All statistical analyses were conducted using R and SAS software.

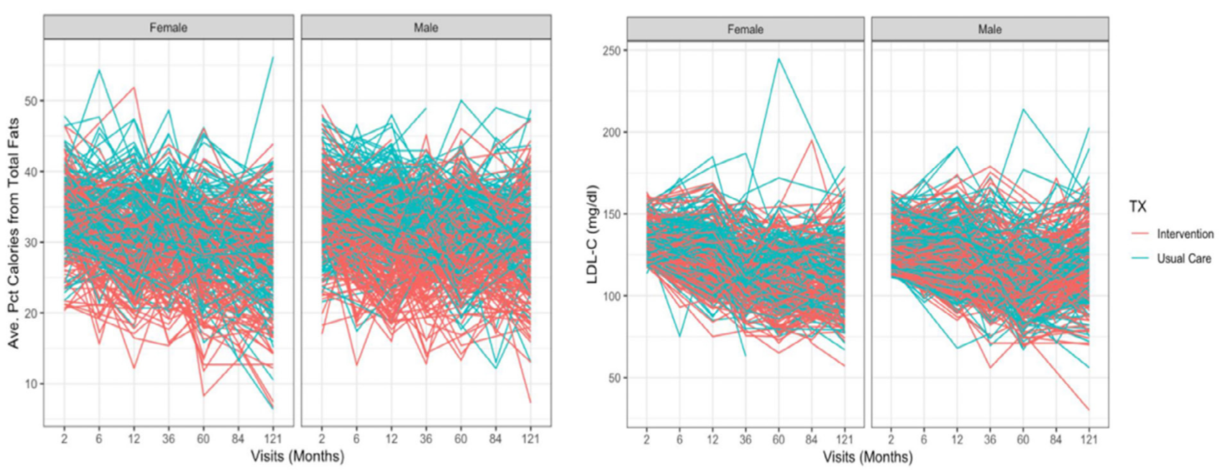
# RESULTS

Mixed effect models were applied to evaluate the effects of the DISC dietary intervention on LDL-C and dietary intake outcomes, including AVE1, AVE3, AVE6, AVE7 and AVE9. The model including a treatment-by-time interaction provided a significantly better fit than the model assuming a constant treatment effect (LRT $p = 0.027$), indicating that the intervention effect on LDL-C varied over time. As shown in Figure 1, individual-level trajectories revealed more pronounced reductions in LDL-C and AVE3 among participants in the intervention group compared to usual care.

The intervention also resulted in early reductions in caloric intake and sustained improvements in dietary fat profiles. While caloric intake rose again at the 36-month mark, likely reflecting age-related growth and increased energy requirements, the intervention group maintained a lower proportion of calories from AVE3 and AVE7 relative to usual care.

Figure 2 illustrates these LDL-C trends over time for both groups. Both groups started with similar estimated mean LDL-C levels (~127–128 mg/dL at 2 months). The intervention group showed a more pronounced early decline, with an estimated difference of approximately 3 mg/dL at 12 months, widening to approximately 5 mg/dL by month 84, before the groups converged toward the last visit. The treatment-by-time interaction was statistically significant (LRT $p = 0.005$), confirming that the intervention effect on

*Figure 1. Individual trajectories of diet and LDL-C by sex and treatment*



LDL-C varied over time, with some variability in later visits potentially driven by developmental hormonal changes during adolescence. Figure 3 shows the AVE3 over time for both groups (LRT $p < 0.0001$). Baseline levels were comparable between groups (~33–34% at 2 months). The intervention group showed a sharp early reduction, dropping to approximately 28% by 6 months, and sustained this lower level throughout the 10-year follow-up, averaging around 28–29% from month 12 onward. The usual care group declined more gradually, from ~34% at 2 months to ~31% by the last visit, resulting in a persistent between-group difference of approximately 3–4 percentage points across most of the follow-up period, suggesting long-term adoption of healthier eating patterns in the intervention group despite some fluctuations likely due to adherence challenges over time. Figure 4 shows the percentage of calories from AVE7 over time over time for both groups (LRT $p < 0.0001$). Starting at similar levels (~12.5–12.8% at 2 months), the intervention group showed a sharp early reduction, dropping to approximately 10.5% by 6 months, compared to ~12.0% in the usual care group. While both groups showed notable fluctuations throughout follow-up, the intervention group consistently maintained lower AVE7 intake, averaging approximately 10–11.5% across visits. Notably, the two groups converged at month 36 (~10.5% each) before diverging again, pointing to the challenges of maintaining strict dietary changes over time, particularly during adolescence.

*Figure 2. Effect of Treatment on LDL over 10 years*

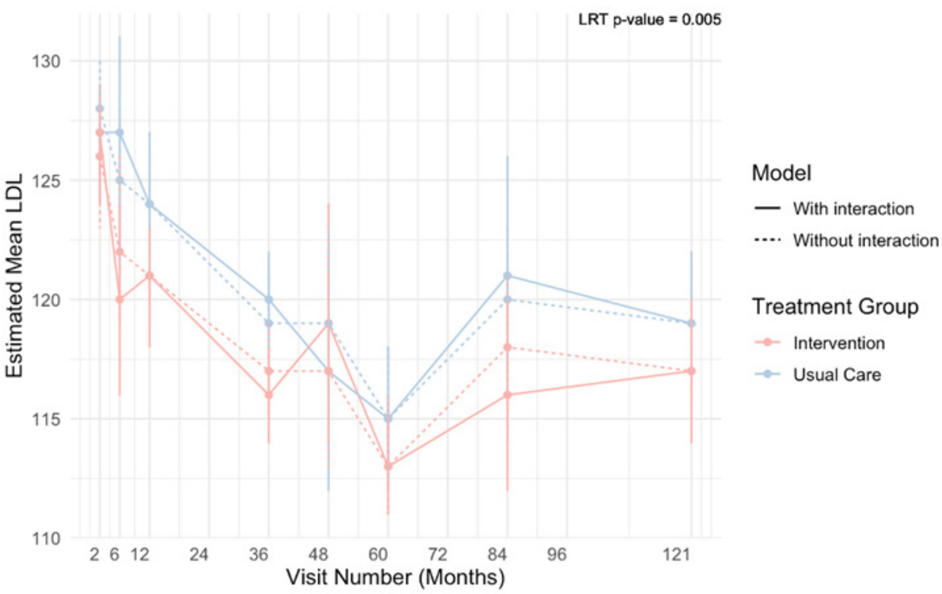



*Figure 3. Effect of Average % calories from total fat over 10 years*

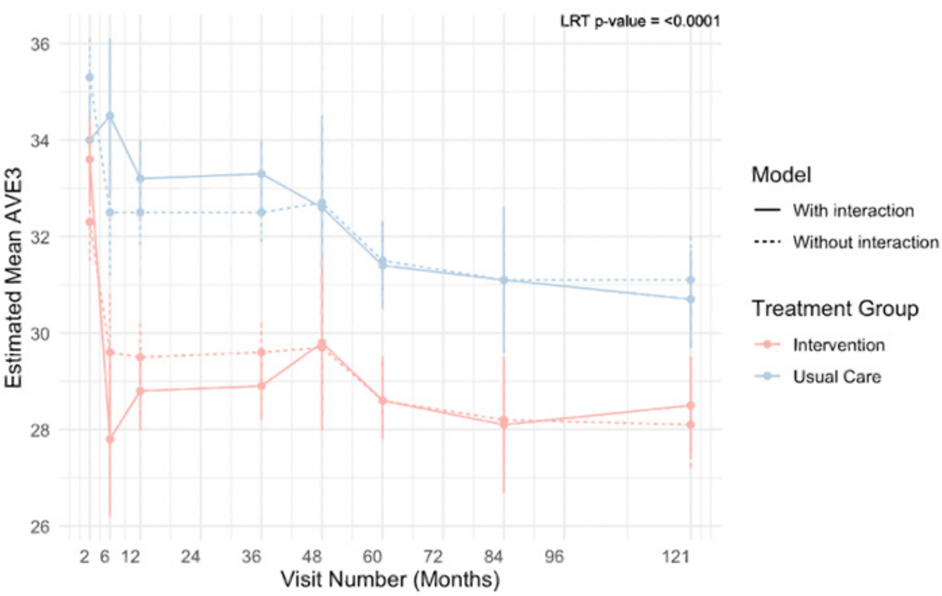
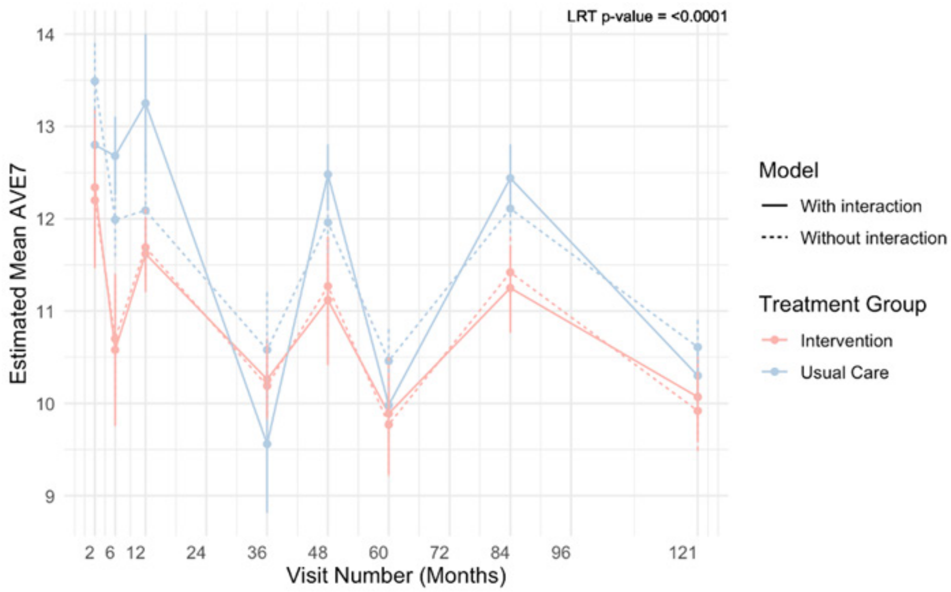


*Figure 4. Effect of Average % calories from Saturated fats over 10 years*




To supplement these findings, spline models were used to explore potential non-linear trends in dietary intake and LDL outcomes. These models supported the patterns observed in the mixed effect models, indicating early intervention effects followed by longer-term stabilization, and confirmed the complex, time-dependent nature of dietary change in children and adolescents.

*Figure 5. Change in LDL by baseline Age and Treatment*

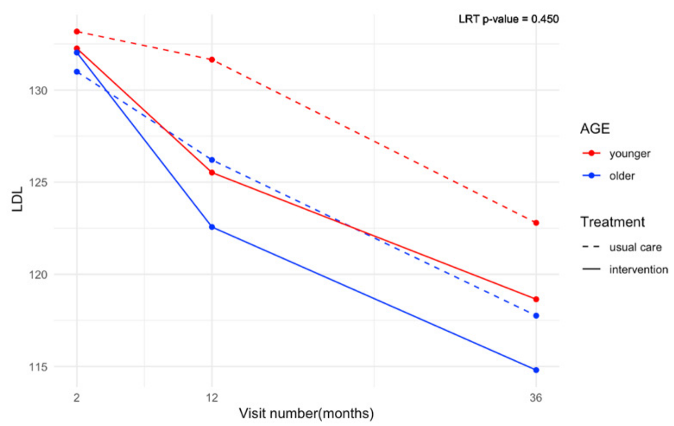
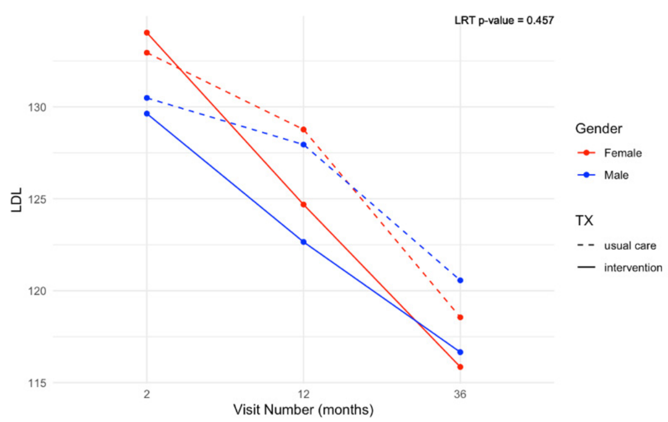



*Figure 6. Change in LDL By Gender and Treatment*



We evaluated the impact of demographic factors and attendance on LDL-C and dietary outcomes. As shown in Figure 5, the intervention led to LDL reductions across both age groups. The older group (solid blue) showed a more pronounced reduction, with estimated mean LDL-C declining from 131 mg/dL at 2 months to 115 mg/dL at 36 months in the intervention arm, compared to 119 mg/dL in the usual care arm. The younger group (solid red) showed a more modest decline, from 133 mg/dL to 123 mg/dL in the intervention arm, compared to 119 mg/dL in usual care. However, the age-by-treatment interaction was not statistically significant (LRT $p = 0.450$), indicating that the differential response by age group should be interpreted with caution. Figure 6 shows that females in the intervention group experienced a greater LDL reduction, declining from 132 mg/dL at 2 months to 119 mg/dL at 36 months, compared to a decline from 129 mg/dL to 129 mg/dL in the usual care group. Males in the intervention group declined from 130 mg/dL to 116 mg/dL, compared to 121 mg/dL in usual care at 36 months. However, the gender-by-treatment interaction was not statistically significant (LRT $p = 0.457$). Attendance at dietary education sessions was significantly associated with improved dietary outcomes. As shown in Table 1, higher attendance was associated with a significant reduction in the AVE3 ($\beta = -1.22$, SE 0.56, $p = 0.029$). Males showed significantly higher baseline AVE3 compared to females ($\beta = 1.16$, SE 0.55, $p = 0.036$). A significant interaction between gender and attendance ($\beta = -2.00$, SE 0.75, $p = 0.003$) indicated that the beneficial effect of attendance on total fat reduction was stronger among males.

*Table 1. The Effect of Higher Attendance on Average % Calories from Total Fats*

| | Estimate | SE | P-value |
|---|---|---|---|
| gender | 1.16 | 0.55 | 0.036* |
| attendance | -1.22 | 0.56 | 0.029* |
| attended parents | -1.28 | 1.55 | 0.410 |
| gender: attendance | -2.00 | 0.75 | 0.003* |

* Significant at 0.05

*Table 2. Effect of Participants' adherence to dietary goals on LDL*

| | Estimate | SE | P-value |
|---|---|---|---|
| gender | -2.01 | 1.06 | 0.058 |
| attendance | -1.42 | 1.11 | 0.200 |
| attended parents | -13.97 | 4.18 | <0.0001* |

* Significant at 0.05

We further assessed how parental involvement influenced LDL-C levels. Table 2 shows that Having at least one parent attend sessions was associated with a 13.97 mg/dL lower LDL-C level ($\beta = -13.97$, SE 4.18, $p < 0.0001$), independent of gender and general attendance. Although male sex and higher general attendance showed trends toward lower LDL-C ($\beta = -2.01$, SE 1.06, $p = 0.058$ and $\beta = -1.42$, SE 1.11, $p = 0.200$, respectively), these effects did not reach statistical significance.

Adherence was also linked to reductions in dietary fat. As shown in Table 3, higher attendance was significantly associated with lower AVE3 ($\beta = -2.24$, SE 0.37, $p < 0.0001$). Greater session attendance was associated with lower saturated-fat intake ($\beta = 0.05$, SE 0.36, $p = 0.883$ and $\beta = -0.78$, SE 1.50, $p = 0.601$, respectively).

Higher attendance was significantly associated with lower AVE7 intake ($\beta = -1.07$, SE 0.18, $p < 0.0001$). Both parental marital status ($\beta = 0.36$, SE 0.36, $p = 0.017$) and parental education level ($\beta = 0.20$, SE 0.06, $p = 0.044$) were significantly associated with greater session attendance, suggesting that family stability and socioeconomic factors play a role in intervention engagement. (See Supplementary Tables S1-S2).

We also examined whether participants met key dietary goals, including reductions in AVE3, AVE7, LDL-C and increases in AVE9. As illustrated in Figure 7 at both 12 and 36 months, the intervention group had a significantly higher proportion of participants meeting AVE3, AVE7, LDL-C targets compared to usual care (all $p < 0.001$). The largest difference was observed for AVE3 at 36 months (Diff of Diff: 31.08, 95% CI: 23.05–39.1) and for LDL-C at 12 months (Diff of Diff: 26.26, 95% CI: 17.57–34.96). In contrast, no significant difference was observed in AVE9 goal attainment at either time point ($p = 0.571$ and $p = 0.892$ at 12 and 36 months, respectively).

*Table 3. Effect of Participants' adherence to dietary goals on Average % Calories from Total Fat*

| | Estimate | SE | P-value |
|---|---|---|---|
| gender | 0.05 | 0.36 | 0.883 |
| attendance | -2.24 | 0.37 | <0.0001* |
| attended parents | -0.78 | 1.50 | 0.601 |

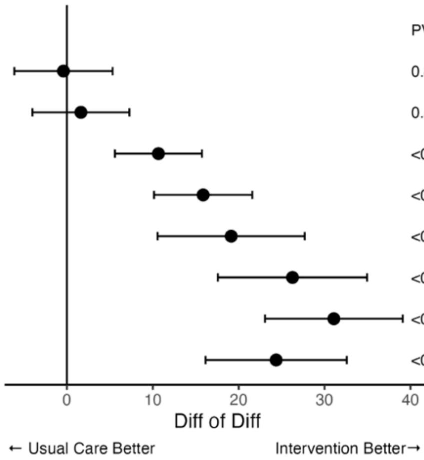
* Significant at 0.05

## DISCUSSION

This reanalysis of the DISC study demonstrates that early dietary interventions can yield sustained reductions in LDL-C and improvements in fat intake among children with elevated lipid levels. The intervention group experienced the most pronounced LDL-C decline during the first 12 months, with effects persisting through year three, consistent with the

*Figure 7. Forest Plot of Change from Baseline to 12 and 36 Months*

| Subgroup | Intervention (SE) | Usual Care (SE) | Diff of Diff (95% CI) | PValue* |
|---|---|---|---|---|
| PUFAs(36m) | -6.02(1.89) | -5.63(2.22) | -0.4 (-6.12,5.32) | 0.892 |
| PUFAs(12m) | -4.57(1.80) | -6.2(2.25) | 1.63 (-4.01,7.28) | 0.571 |
| SAT fat(36m) | 11.07(2.41) | 0.41(0.94) | 10.66 (5.59,15.72) | <0.001 |
| SAT fat(12m) | 17.88(2.67) | 2.02(1.17) | 15.86 (10.14,21.58) | <0.001 |
| cholesterol(36m) | 20.02(3.16) | 0.89(3.01) | 19.13 (10.56,27.69) | <0.001 |
| cholesterol(12m) | 26.72(3.27) | 0.45(2.99) | 26.26 (17.57,34.96) | <0.001 |
| total fat(36m) | 32.12(3.29) | 1.04(2.44) | 31.08 (23.05,39.1) | <0.001 |
| total fat(12m) | 29.22(3.28) | 4.86(2.62) | 24.36 (16.14,32.59) | <0.001 |




original DISC trial findings [1]. These trends were further validated through spline models, which captured complex, non-linear patterns in dietary change. Notably, the significant treatment-by-time interaction (LRT p = 0.005) revealed that the intervention effect was not constant but followed a non-linear trajectory, with the greatest between-group differences observed during the early intensive intervention phase and a gradual convergence in later years as intervention intensity decreased. This pattern suggests that the timing and intensity of dietary counseling are critical determinants of sustained lipid-lowering effects, and that maintenance strategies may be needed to preserve early gains as children transition into adolescence.

The application of linear mixed-effects and spline models in this reanalysis offered methodological advantages over the original DISC analyses, which relied primarily on analysis of covariance at discrete time points. By modeling the full longitudinal trajectory of LDL-C and dietary outcomes, these approaches captured the dynamic and non-linear nature of dietary change across childhood and adolescence. In particular, B-spline models revealed complex patterns in fat and caloric intake that would not have been detectable using traditional repeated-measures approaches, providing a more nuanced understanding of how dietary behavior evolves over time in response to intervention. This methodological approach is consistent with growing recommendations to apply flexible longitudinal models in pediatric clinical trial re-analyses to better characterize individual-level trajectories [11, 12].

Although age was not statistically significantly associated with LDL-C reduction (p = 0.45), older children appeared to experience a somewhat greater initial response to the intervention. This pattern is consistent with contemporary perspectives on heterogeneous treatment effects and the need to look beyond average treatment effects to identify subgroups with differential benefit [16]. The lack of statistical significance may reflect limited power to detect subgroup differences rather than a true absence of effect, and future studies with larger samples should examine whether age at intervention initiation moderates long-term cardiovascular outcomes. Similarly, females exhibited larger reductions in LDL-C than males. This pattern is in line with observations from the Harvard Growth Study, which point to gender-based differences in fat metabolism and response to dietary exposures [17]. This finding partly reflect the well-documented tendency for boys to have less favorable baseline dietary patterns than girls, including higher fat intake and lower consumption of health-promoting foods [18, 19], which could limit the magnitude of dietary change achievable in male participants. These findings collectively suggest that intervention strategies tailored to age and sex may enhance long-term effectiveness.

Adherence emerged as a critical driver of intervention success. Participants with higher session attendance showed significantly better dietary outcomes, particularly reductions in AVE1 and AVE7 intake (p < 0.0001). Moreover, parental attendance at sessions was associated with a substantial LDL-C reduction (p < 0.0001), highlighting the importance of family involvement in behavioral interventions. A systematic review of interventions to improve children's diet found that studies with high parental involvement were associated with statistically significant improvements in dietary practices, with direct methods of parental involvement, including attendance at educational and behavioral counseling sessions, showing the most promise in improving child dietary outcomes [20, 21].These findings echo those of Murray and Hernán, who emphasized the role of adherence as both a behavioral marker and a modifier of treatment effect [22], and reinforce the conclusion that engaging parents as active participants rather than passive observers substantially amplifies the impact of dietary counseling programs.

Socioeconomic factors also influenced engagement. Parental marital stability and higher education levels were associated with greater session attendance ($p = 0.017$ and $p = 0.044$, respectively), mirroring trends observed in the Look AHEAD trial, where education and marital status predicted adherence and lifestyle change success [23]. These findings are consistent with broader evidence, a study evaluating predictors of parent engagement in a family-based childhood obesity prevention program found that married parents and those with higher education showed significantly greater attendance at intervention sessions [24]. Furthermore, a prospective birth cohort study found that higher maternal education at the child's birth was independently associated with greater adherence to a healthy dietary pattern at school age [25], suggesting that the influence of parental education extends beyond intervention attendance to shaping the overall dietary environment at home. These findings highlight a potential equity concern, children from less educated or single-parent households may be systematically less likely to benefit from standard dietary intervention programs.

Interestingly, although the intervention group had higher adherence to goals for AVE3, AVE7 and LDL-C intake at both 12 and 36 months (all $p < 0.001$), no significant difference was observed in AVE9 goal attainment. This likely reflects the distinct behavioral demands of each dietary goal, reducing AVE7 and LDL-C can often be achieved through avoidance and substitution strategies, whereas increasing PUFA intake requires more deliberate dietary additions such as fish, nuts, and plant-based oils that may be less familiar or accessible to families, as suggested by similar findings in the STRIP Baby Project [26]. This challenge is not unique to DISC. A global review of fat intake data from 65 studies across 33 countries found that omega-3 PUFA intake, particularly DHA, was below international recommendations in most studies of children, suggesting that inadequate PUFA intake is a widespread and persistent challenge across diverse populations and intervention contexts [27]. Furthermore, a systematic review of dietary fat interventions in children found that evidence for the benefit of increasing PUFA intake on LDL-C was more variable and less consistent than the evidence for reducing AVE7 and LDL-C, particularly in girls [28], suggesting that PUFA-specific goals may require more targeted behavioral strategies beyond general dietary counseling.

Altogether, these findings underscore the multifactorial nature of successful dietary interventions in children. Intensive early intervention appears critical for achieving meaningful LDL-C reductions, and maintenance strategies should be built into program design to preserve early gains through adolescence. Family-based components, particularly parental attendance, should be considered a core element of pediatric dietary programs, and sociodemographic barriers to participation must be actively addressed to ensure equitable access to intervention benefits. Future interventions should also incorporate more targeted behavioral strategies to support PUFA intake, alongside the more achievable goals of reducing AVE7 and LDL-C. Ultimately, personalized, family-centered, and equity-conscious approaches offer the greatest promise for reducing cardiovascular risk from the earliest stages of life.

### Strength and Limitation

A key strength of this study is the application of advanced longitudinal modeling methods to a well-characterized randomized trial dataset, enabling a more nuanced characterization of intervention effects over time than was possible in the original analyses. However, this study also has some limitations. As a secondary analysis of the DISC trial, we were limited to the variables and measurements originally collected, which constrained our ability to account for unmeasured confounders or refine certain outcome assessments. In addition, dietary intake was based on self-reported data, which is subject to recall bias and misreporting, particularly among children.

## CONCLUSION

This reanalysis of the DISC trial demonstrates that a family-based dietary intervention initiated in childhood can produce meaningful reductions in LDL-C and sustained improvements in dietary fat intake. The effectiveness of the intervention was strongly modulated by parental involvement, session attendance, and sociodemographic factors, highlighting the importance of family-centered and equity-conscious approaches in pediatric cardiovascular health programs. These findings reinforce the value of early, personalized dietary intervention as a strategy for reducing lifetime cardiovascular risk.

## ETHICS COMMITTEE APPROVAL

The original DISC was a randomized, controlled trial conducted at six clinical centers with oversight from a coordinating center and project office. The trial protocol was approved by the institutional review boards of all participating centers, and trial conduct was monitored by an independent data and safety monitoring committee appointed by the National Heart, Lung, and Blood Institute. The present secondary analysis of de-identified DISC data was reviewed and approved by the University of Massachusetts Chan Medical School Institutional Review Board, and additional informed consent was not required.

## TRIAL REGISTRATION

NCT00000459

## INFORMED CONSENT

Written informed consent was obtained from parents or legal guardians, with assent from children when appropriate, in the original DISC trial. Additional informed consent was not required for this secondary analysis of de-identified data.

## DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article. DOI: 10.13130/RD_UNIMI/JPFBFI

## AUTHORSHIP CONTRIBUTIONS

Conceptualization: A.S., R.B.
Methodology: A.S., R.B.
Formal Analysis: A.S
Statistical Consultation/Validation: B.B., R.B.
Visualization: A.S.
Writing the Original Draft: A.S
Writing the Review & Editing: B.B., R.B.
Supervision: B.B
(All authors reviewed and approved the final manuscript.)

## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

## FINANCIAL DISCLOSURE

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