Early Childhood Investments Substantially Boost Adult Health

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Early Childhood Investments Substantially Boost Adult Health

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High-quality early childhood programs have been shown to have substantial benefits in reducing crime, raising earnings, and promoting education. Much less is known about their benefits for adult health. We report on the long-term health effects of one of the oldest and most heavily cited early childhood interventions with long-term follow-up evaluated by the method of randomization: the Carolina Abecedarian Project (ABC). Using recently collected biomedical data, we find that disadvantaged children randomly assigned to treatment have significantly lower prevalence of risk factors for cardiovascular and metabolic diseases in their mid-30s. The evidence is especially strong for males. The mean systolic blood pressure among the control males is 143 millimeters of mercury (mm Hg), whereas it is only 126 mm Hg among the treated. One in four males in the control group is affected by metabolic syndrome, whereas none in the treatment group are affected. To reach these conclusions, we address several statistical challenges. We use exact permutation tests to account for small sample sizes and conduct a parallel bootstrap confidence interval analysis to confirm the permutation analysis. We adjust inference to account for the multiple hypotheses tested and for nonrandom attrition. Our evidence shows the potential of early life interventions for preventing disease and promoting health.

Noncommunicable diseases are responsible for roughly two-thirds of worldwide deaths (*1*). Most policies that combat disease currently focus on treatment after disease occurs and on reducing risk factors in adult life. Recent discussions of effective ways of controlling the soaring costs of the U.S. health care system emphasize tertiary prevention—that is, reducing the worsening of the conditions of those already ill [see, e.g., (*2*)] and "bending the cost curve" for such treatments (*2*–*5*).

A complementary approach is to prevent disease or to delay its onset. A large body of evidence shows that adult illnesses are more prevalent and problematic among those who have experienced adverse early life conditions (*6*, *7*). The exact mechanisms through which early life experiences translate into later life health are being actively investigated (*8*, *9*).

This paper shows that high-quality, intensive interventions in the early years can be effective in preventing, or at least delaying, the onset of adult disease. The recent literature establishes that interventions that enrich the environments of disadvantaged children have substantial impacts on a variety of outcomes throughout their lives [see, e.g., (*10*–*12*)]. However, little is known about their benefits on health [see, e.g., (*13*)].

We study the long-term health effects of one of the oldest and most cited early childhood programs: the Carolina Abecedarian Project (ABC). ABC was designed as a social experiment to investigate whether a stimulating early childhood environment could prevent the development of mild mental retardation in disadvantaged children. The study was conducted on four cohorts of disadvantaged children born between 1972 and 1977 who were living in or near Chapel Hill, North Carolina. The base sample included 109 families (111 children). Of these 111 children, 57 were assigned to treatment status and 54 were assigned to control status. The intervention consisted of a two-stage treatment targeted to different segments of child life cycles: an early childhood stage (from birth through age 5) and a subsequent school-age stage (from age 6 through 8). The first stage of the intervention involved periods of cognitive and social stimulation interspersed with caregiving and supervised play throughout a full 8-hour day for the first 5 years. The stimulation component was based on a curriculum that emphasized development of language, emotional regulation, and cognitive skills (*14*, *15*). The second stage of the intervention focused on improving early math and reading skills through having "home-school resource teachers" customize learning activities based on materials being covered at school and then deliver these materials to the parents to use at home. The treatment and control groups from the first stage were randomly assigned to treatment and control groups in the second stage. We analyzed data on treatment and control groups created by the first-stage randomization. We found no evidence of any treatment effect on adult health from the second-stage randomization. The treatment effects are much smaller in magnitude than those estimated for the first-stage treatment and fail to achieve statistical significance at conventional levels. See the supplementary materials, section F, for evidence on this issue. References (*16*–*18*) show that for most outcomes the early educational intervention had much stronger effects than the school-age treatment. Additionally, previous work has also shown no health effects from a school-age (as compared with a preschool) educational intervention (*19*). The available evidence on interventions to prevent obesity points to the years 0 through 5 as a critical period (as compared with after 5 years) [see, e.g., (*20*–*22*)].

The ABC intervention also had a nutritional and health care component during the first stage. Treated children had two meals and a snack at the childcare center. They were offered primary pediatric care (both well- and ill-child care), with periodic check-ups and daily screening. More details on the intervention are given in the supplementary materials, section A.

Data

Data were collected on both treated and control cases from the beginning of their participation in the study, using surveys administered to children, parents, and teachers, as well as direct assessments. Before the intervention started, baseline information was gathered on parental characteristics, family structure, socioeconomic status, and birth circumstances. For both treated and control cases, data on cognition, personality, health, achievement, and behavior were then collected at multiple stages from birth until the end of school-age treatment. At the end of the second stage of treatment, participants were followed up at ages 12, 15, 21, 30, and in the mid-30s. Details on the outcomes and covariates used in this analysis are provided in the supplementary materials, section B.

A biomedical survey of cardiovascular and metabolic risk factors was conducted when participants were in their mid-30s. Information on biomeasures was collected from two sources. The first source was a physical exam carried out by a local physician in the Chapel Hill Internal Medicine practice, in which the same doctor (blind to treatment status) examined all subjects. In this exam, measurements were collected on weight (pounds), height (inches), waist (inches), hips (inches), and systolic and diastolic blood pressure (bp). The physician also checked the status of several body systems. The physician carried out a complete physical exam and checked whether there was abnormality in relation to the following systems: skin, HEENT (head, ear, eye, nose, and throat), neck, chest, lung, breast, cardiovascular, abdomen, neurologic, muscle strength and tone, musculoskeletal, and lymphatic. The second source was laboratory tests, based on nonfasting venous blood collected from the subjects during the medical visit (the phlebotomist was blind to treatment status, and the blood samples were sent out to another facility for analysis and report preparation).

Several issues arise in evaluating the health effects of the ABC intervention. First, the sample size is small. Conventional testing approaches that rely on large-sample properties of test statistics

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may be inappropriate. To surmount this problem, we use exact (small-sample) block permutation tests. We show in tables S25 and S26 that when we use bootstrap methods that have a large sample justification, we obtain the same inference about treatment effects. Bootstrapping has the additional benefit of producing confidence intervals to gauge the uncertainty inherent in our estimates.

Second, numerous treatment effects are analyzed. This creates an opportunity for "cherry picking"—finding spurious treatment effects merely by chance if conventional one-hypothesis-at-a-time approaches to testing are used. We account for the multiplicity of the hypotheses being tested using recently developed stepdown procedures (*23*).

Third, information is missing due to nonrandom attrition from the survey, potentially undermining the validity of inference. We investigate the causes of missing information and correct for potential bias using inverse probability weighting (IPW) (*24*, *25*). More information on the methodology and a detailed analysis of the attrition patterns is presented in the supplementary materials, sections C, D, and H.

Results

Physical Health

Estimated treatment effects and associated test statistics are given in Tables 1 (males) and 2 (females). Throughout the paper, we report one-sided single-hypothesis block permutation *P* values associated with the IPW treatment effect estimates; multiple hypothesis stepdown *P* values are reported in Tables 1 and 2. We first report the experimental results on the biomarkers of cardiovascular functioning. On average, treated males have lower values of both systolic and diastolic bp. This difference amounts to 13.5 mm Hg for diastolic bp ($P = 0.024$) and 17.5 mm Hg for systolic bp ($P = 0.018$). Treated females are less likely to be prehypertensive. The prevalence of prehypertension (systolic bp $\geq$ 120 or diastolic bp $\geq$ 80) (*26*) is 0.909 in the control group and 0.667 in the treatment group, and the difference is statistically significant ($P = 0.042$). Using two different definitions of hypertension [systolic bp $\geq$ 140 and diastolic bp $\geq$ 90 (*27*) and systolic bp $\geq$ 140 or diastolic bp $\geq$ 90 (*26*)], treated males are less likely to fall into the stage I hypertension category (a prevalence of only 0.105 or 0.211) as compared with a much higher prevalence observed in the control group (0.444 and 0.556). Both treatment effects are statistically significant ($P = 0.010$ and $P = 0.038$) (*28*).

Table 1. ABC intervention, males: main health results, biomedical sweep. This table presents the inference and descriptive statistics of selected outcomes of the ABC intervention. The first column describes the outcome analyzed. The remaining six columns present the statistical analysis. The columns present the following information: (i) Control mean. (ii) Treatment mean. (iii) Unconditional difference in means across treatment and control groups. We multiply the difference in means by (−1) when a higher value of the variable in the raw data represents a worse outcome so that all outcomes are normalized in a favorable direction (but are not restricted to be positive). (iv) Conditional treatment effect controlling for cohort, number of siblings, mother's IQ, and high-risk index at birth, and accounting for attrition using IPW. Probabilities of IPW are estimated using the following variables: prematurity (gestational age < 37 weeks), a dichotomous indicator for not having an exam for illness or injury in the past 2 years at age 30, Achenbach DSM attention-deficit/hyperactivity (AD/H) problems scale at age 30, and Achenbach substance abuse scale at age 30. The selection of covariates for IPW is based on the lowest Akaike Information Criteria (AIC) among models examining all combinations of covariates that present statistically significant imbalance between attriters and nonattriters. See supplementary materials section C and table S1 for details. (v) One-sided single-hypothesis block permutation *P* value associated with the IPW treatment effect estimate. By block permutation, we mean that permutations are done within strata defined by the preprogram variables used in the randomization protocol: cohort, gender, number of siblings, mother's IQ, and high-risk index. (vi) Multiple hypothesis stepdown *P* values associated with (v). The multiple hypothesis testing is applied to blocks of outcomes. Blocks of variables that are tested jointly using the stepdown algorithm are delineated by horizontal lines. *P* values $\leq$ 0.10 are in bold type. HbA1C, glycosylated hemoglobin; NCEP, National Cholesterol Education Program. See table S11 for complete estimation results.

Variable	Control mean	Treatment mean	Difference in means	Conditional treatment effect	Block *P* value	Stepdown *P* value
			Blood pressure			
Diastolic blood pressure (mm Hg)	92.000	78.526	13.474	19.220	**0.024**	**0.024**
Systolic blood pressure (mm Hg)	143.333	125.789	17.544	24.828	**0.018**	**0.029**
Prehypertension (systolic bp $\geq$ 120 and diastolic bp $\geq$ 80)	0.667	0.421	0.246	0.321	0.119	0.172
Prehypertension (systolic bp $\geq$ 120 or diastolic bp $\geq$ 80)	0.778	0.684	0.094	0.096	0.235	0.235
Hypertension (systolic bp $\geq$ 140 and diastolic bp $\geq$ 90)	0.444	0.105	0.339	0.537	**0.010**	**0.018**
Hypertension (systolic bp $\geq$ 140 or diastolic bp $\geq$ 90)	0.556	0.211	0.345	0.404	**0.038**	**0.038**
			Laboratory tests			
High-density lipoprotein (HDL) cholesterol (mg/dL)	42.000	53.211	11.211	11.720	**0.066**	0.110
Dyslipidemia (HDL < 40 mg/dL)	0.417	0.106	0.311	0.255	0.179	0.179
Prediabetes (HbA1C $\geq$ 5.7%)	0.583	0.473	0.110	0.043	0.426	0.426
Vitamin D deficiency (<20 ng/mL)	0.750	0.368	0.382	0.435	**0.021**	**0.021**
			Obesity			
Overweight (BMI $\geq$ 25)	0.750	0.722	0.028	0.190	0.239	0.239
Obese (BMI $\geq$ 30)	0.625	0.556	0.069	0.211	0.233	0.345
Severely obese (BMI $\geq$ 35)	0.375	0.111	0.264	0.404	0.115	0.232
Waist-hip ratio (WHR)	0.962	0.937	0.025	0.045	0.293	0.293
Abdominal obesity (WHR > 0.9)	0.875	0.647	0.228	0.294	0.137	0.218
			Multiple risk factors			
Obesity and hypertension	0.500	0.111	0.389	0.529	**0.016**	**0.016**
Severe obesity and hypertension	0.375	0.000	0.375	0.502	**0.005**	**0.012**
Hypertension and dyslipidemia	0.333	0.000	0.333	0.435	**0.006**	**0.012**
Metabolic syndrome (NCEP definition)	0.250	0.000	0.250	0.465	**0.007**	**0.014**
Framingham risk score (*34*)	7.043	4.889	2.154	3.253	**0.038**	**0.038**

Biomarkers of metabolic activity from blood tests (lipid panel) show that treated individuals have higher levels of high-density lipoprotein cholesterol (HDL-C)—"good" cholesterol. The magnitude of the difference between treated and control groups is larger for males. The control males have a level of HDL cholesterol of 42 mg/dL, which is just above the lower recommended limit of 40 mg/dL (*29*), whereas the level for the treated males is 11 mg/dL higher. The treatment effect is marginally significant ($P = 0.066$). This is reflected in the prevalence of dyslipidemia (elevated lipid levels). The difference in the prevalence of this condition between treatment and control groups is 0.311 for males (HDL-C < 40 mg/dL; $P = 0.179$) and 0.177 for females (HDL-C < 50 mg/dL; $P = 0.099$). The healthier metabolic status experienced by the male treatment group is confirmed by the lower prevalence of pre-diabetes indicators [glycosylated hemoglobin ≥ 5.7% (*30*), 0.473 versus 0.583], although the difference does not attain statistical significance ($P = 0.426$). Control males are also twice as likely to be affected by vitamin D deficiency (total vitamin D < 20 ng/mL (*31*); 0.368 versus 0.750; $P = 0.021$).

The prevalence of both severe and abdominal obesity is lower among treatment group males but the differences are not statistically significant at the 10% level. Treated females are less likely than controls to be affected by abdominal obesity, both when considering the waist-hip ratio (WHR) and when analyzing a dichotomous measure of WHR > 0.85 (*32*) (0.563 versus 0.762); both treatment effects are marginally significant ($P = 0.063$ and $P = 0.080$, respectively).

The health effects of the ABC intervention translate into lower prevalence of multiple risk factors that are particularly striking for males. Those in the treatment group are less likely to experience both obesity and hypertension [difference in mean (diff.) = 0.389; $P = 0.016$], severe obesity and hypertension (diff. = 0.375; $P = 0.005$), and dyslipidemia and hypertension (diff. = 0.333; $P = 0.006$). None of the treated males have the cluster of conditions known as metabolic syndrome [defined as waist circumference > 102 cm or 40 inches (*33*); HDL-C < 40 mg/dL; bp ≥ 130/85 mm Hg (*29*)], associated with greater risk of heart disease, stroke, and diabetes, whereas one in four in the control group is affected by it ($P = 0.007$). The prevalence of the metabolic syndrome for females [defined as waist circumference > 88 cm or 35 inches (*33*); HDL-C < 50 mg/dL; bp ≥ 130/85 mm Hg (*29*)] is lower in the treatment group, but the differences are not statistically significant at the 10% level. Finally, results for the Framingham

Table 2. ABC intervention, females: main health results, biomedical sweep. This table presents the inference and descriptive statistics of selected outcomes of the ABC intervention. The first column describes the outcome analyzed. The remaining six columns present the statistical analysis. The columns present the following information: (i) Control mean. (ii) Treatment mean. (iii) Unconditional difference in means across treatment and control groups. We multiply the difference in means by (–1) when a higher value of the variable in the raw data represents a worse outcome so that all outcomes are normalized in a favorable direction (but are not restricted to be positive). (iv) Conditional treatment effect controlling for cohort, number of siblings, mother's IQ, and high-risk index at birth, and accounting for attrition using IPW. Probabilities of IPW are estimated using the following variables for the biomedical sweep outcomes: prematurity (gestational age <37 weeks), mother Wechsler Adult Intelligence Scale (WAIS) digit symbol score at recruitment, Achenbach rule-breaking problem scale at age 30, and Achenbach substance abuse scale at age 30. The selection of covariates for IPW is based on the lowest AIC among models examining all combinations of covariates that present statistically significant imbalance between attriters and non-attriters. See supplementary materials section C and table S2 for details. (v) One-sided single-hypothesis block permutation *P* value associated with the IPW treatment effect estimate. By block permutation, we mean that permutations are done within strata defined by the preprogram variables used in the randomization protocol: cohort, gender, number of siblings, mother's IQ, and high-risk index. (vi) Multiple hypothesis stepdown *P* values associated with (v). The multiple hypothesis testing is applied to blocks of outcomes. Blocks of variables that are tested jointly using the stepdown algorithm are delineated by horizontal lines. *P* values ≤ 0.10 are in bold type. See table S12 for complete estimation results.

Variable	Control mean	Treatment mean	Difference in means	Conditional treatment effect	Block *P* value	Stepdown *P* value
			Blood pressure			
Diastolic blood pressure (mm Hg)	89.227	85.333	3.894	1.204	0.446	0.446
Systolic blood pressure (mm Hg)	135.636	129.666	5.970	2.185	0.300	0.380
Prehypertension (systolic bp ≥ 120 and diastolic bp ≥80)	0.727	0.500	0.227	0.101	0.222	0.222
Prehypertension (systolic bp ≥ 120 or diastolic bp ≥80)	0.909	0.667	0.242	0.244	**0.042**	**0.069**
Hypertension (systolic bp ≥ 140 and diastolic bp ≥ 90)	0.318	0.222	0.096	–0.003	0.375	0.499
Hypertension (systolic bp ≥ 140 or diastolic bp ≥ 90)	0.409	0.500	–0.091	–0.181	0.721	0.721
			Laboratory tests			
High-density lipoprotein (HDL) cholesterol (mg/dL)	55.318	60.444	5.126	6.002	0.143	0.143
Dyslipidemia (HDL < 50 mg/dL)	0.455	0.278	0.177	0.201	**0.099**	0.147
Prediabetes (HbA1C ≥ 5.7%)	0.364	0.353	0.011	0.070	0.580	0.580
Vitamin D deficiency (<20 ng/mL)	0.727	0.722	0.005	0.048	0.303	0.303
			Obesity			
Overweight (BMI ≥ 25)	0.955	0.889	0.066	0.054	0.482	0.690
Obese (BMI ≥ 30)	0.727	0.666	0.061	–0.112	0.790	0.790
Severely obese (BMI ≥ 35)	0.364	0.223	0.141	0.143	0.354	0.653
Waist-hip ratio (WHR)	0.933	0.876	0.057	0.053	**0.063**	0.101
Abdominal obesity (WHR > 0.85)	0.762	0.563	0.199	0.198	**0.080**	**0.080**
			Multiple risk factors			
Obesity and hypertension	0.364	0.278	0.086	–0.028	0.501	0.641
Severe obesity and hypertension	0.136	0.167	–0.031	–0.066	0.696	0.696
Hypertension and dyslipidemia	0.182	0.167	0.015	–0.043	0.486	0.725
Metabolic syndrome (NCEP definition)	0.190	0.062	0.128	0.057	0.184	0.393
Framingham risk score (*34*)	1.482	1.143	0.339	0.331	**0.070**	**0.070**

risk score (*34*) reveal that both treated males and females have a significantly lower risk of experiencing "total" coronary heart disease (CHD), defined as both stable and unstable angina, myocardial infarction, or CHD death, within the next 10 years (diff. = 2.154, $P = 0.038$ for males; diff. = 0.339, $P = 0.070$ for females).

In sum, the available evidence from the biomedical survey of ABC shows that the children who attended the child care center in the first 5 years of their lives enjoy better physical health in their mid-30s, with significant markers indicating better future health. The benefits of these health improvements are substantial and wide-ranging. Reference (*35*) provides a detailed review of the labor market costs of obesity, which range from increased absenteeism to lower productivity and wages. There are considerable losses in life expectancy due to obesity. Reference (*36*) reports estimates that 35-year-old males with hypertension would gain 1.1 to 5.3 years of expected life (0.9 to 5.7 years for females) from reducing their diastolic bp to 88 mm Hg using the Coronary Heart Disease Policy Model based on data from the Framingham Heart Study. Reference (*37*), using data from the Framingham Heart Study, finds that 40-year-old male nonsmokers suffer a loss of life expectancy of 3.1 years (3.3 years for females) because of being overweight, and of 5.8 years (7.1 years for females) because of obesity. Reference (*38*), using data from the National Longitudinal Study of Adolescent Health, shows that diabetics are less likely to be employed (by 8 to 11 percentage points), are more likely to participate in social programs (by 8 to 13 percentage points), and earn on average lower wages (by $1500 to $6000). Reference (*39*) provides further evidence from the National Longitudinal Survey of Youth 1979 that the duration of diabetes is negatively associated with employment and wages. Reference (*40*) reports a hazard ratio of 1.47 (95% confidence interval of 1.13 to 1.92) for all-cause mortality and of 2.53 (95% CI of 1.74 to 3.67) for cardiovascular mortality caused by metabolic syndrome (NCEP definition) in the San Antonio Heart Study.

Health Care

Availability of health care is a necessary condition for enjoying better health, although not a sufficient one (*41*). The upper panel of Table 3 reveals that treated males were more likely to be covered by health insurance at age 30 (0.704 versus 0.476; $P = 0.039$) and to be cared for in a hospital or by a doctor when sick (0.815 versus 0.524; $P = 0.037$). There are no significant differences in the effect of the treatment for females (upper panel of Table 4).

Physical Development

We analyze the effects of the intervention on early physical development, assessed using anthropometric measurements (height and weight) taken when the children had their routine assessments at multiple times in childhood. We transform the body mass index (BMI) measures into standard normal variates (z scores) using the lambda-mu-sigma (LMS) method developed in (*42*–*44*). The results are reported in the bottom panel of Table 3. Treated males were less likely than controls to be overweight throughout their preschool years, with almost no treated child having a weight-for-length above the 85th percentile [the age-specific measure for being "at-risk overweight" (*45*)] in the first 2 years of life. Control males had a greater weight-for-length z-score change between birth and 24 months of age. More rapid increases in weight-for-length in the first 6 months of life have been associated with increased risk of obesity at age 3 (*46*). Looking at the full BMI distribution by treatment status for males shown in Fig. 1, it is evident that the distribution is both less spread out and shifted to the left for treated males relative to controls. These results are consistent with the obesity-reducing effects found in Head Start (*47*, *48*) and are consistent with evidence in the literature of the important role played by early-life nutrition (*49*). Further evidence on the

Table 3. ABC intervention, males: health care at age 30; physical development in childhood. This table presents the inference and descriptive statistics of selected outcomes of the ABC intervention. The first column describes the outcome analyzed. The remaining six columns present the statistical analysis. The columns present the following information: (i) Control mean. (ii) Treatment mean. (iii) Unconditional difference in means across treatment and control groups. We multiply the difference in means by (−1) when a higher value of the variable in the raw data represents a worse outcome so that all outcomes are normalized in a favorable direction (but are not restricted to be positive). (iv) Conditional treatment effect controlling for cohort, number of siblings, mother's IQ, and high-risk index at birth, and accounting for attrition using IPW. The selection of covariates for IPW is based on the lowest AIC among models examining all combinations of covariates that present statistically significant imbalance between attriters and non-attriters. See supplementary materials section C and table S1 for details. (v) One-sided single-hypothesis block permutation P value associated with the IPW treatment effect estimate. By block permutation, we mean that permutations are done within strata defined by the preprogram variables used in the randomization protocol: cohort, gender, number of siblings, mother's IQ, and high-risk index. (vi) Multiple hypothesis stepdown P values associated with (v). The multiple hypothesis testing is applied to blocks of outcomes. Blocks of variables that are tested jointly using the stepdown algorithm are delineated by horizontal lines. P values ≤ 0.10 are in bold type. CDC, Centers for Disease Control and Prevention. WHO, World Health Organization. We use weight-for-length $\geq$ 85th percentile for being "at-risk overweight" under 24 months and BMI-for-age $\geq$ 85th percentile for being overweight for 24 months and older (*45*). See table S13 for complete estimation results.

Variable	Control mean	Treatment mean	Difference in means	Conditional treatment effect	Block P value	Stepdown P value
			Health care at age 30			
Health insurance coverage at age 30	0.476	0.704	0.228	0.226	**0.039**	**0.039**
Buys health insurance at age 30	0.333	0.630	0.296	0.248	**0.035**	**0.080**
Hospital or doctor office care when sick at age 30	0.524	0.815	0.291	0.265	**0.037**	**0.068**
			Physical development in childhood			
At risk overweight (CDC) at 3 months	0.227	0.037	0.190	0.206	**0.026**	0.121
At risk overweight (CDC) at 6 months	0.250	0.080	0.170	0.205	**0.074**	0.182
At risk overweight (CDC) at 9 months	0.412	0.000	0.412	0.446	**0.004**	**0.023**
At risk overweight (CDC) at 12 months	0.429	0.000	0.429	0.408	**0.001**	**0.009**
At risk overweight (CDC) at 18 months	0.389	0.000	0.389	0.385	**0.000**	**0.004**
Overweight (CDC) at 24 months	0.333	0.000	0.333	0.343	**0.001**	**0.011**
Overweight (CDC) at 36 months	0.158	0.080	0.078	0.094	0.194	0.194
Overweight (CDC) at 48 months	0.300	0.167	0.133	0.133	0.150	0.235
Overweight (CDC) at 60 months	0.300	0.125	0.175	0.187	**0.058**	0.179
Overweight (CDC) at 96 months	0.421	0.120	0.301	0.286	**0.030**	0.117
Weight-for-length change 0–24 months (CDC)	0.858	−0.105	0.963	1.176	**0.058**	**0.058**
Weight-for-length change 0–24 months (WHO)	1.265	0.166	1.100	1.397	**0.049**	**0.057**

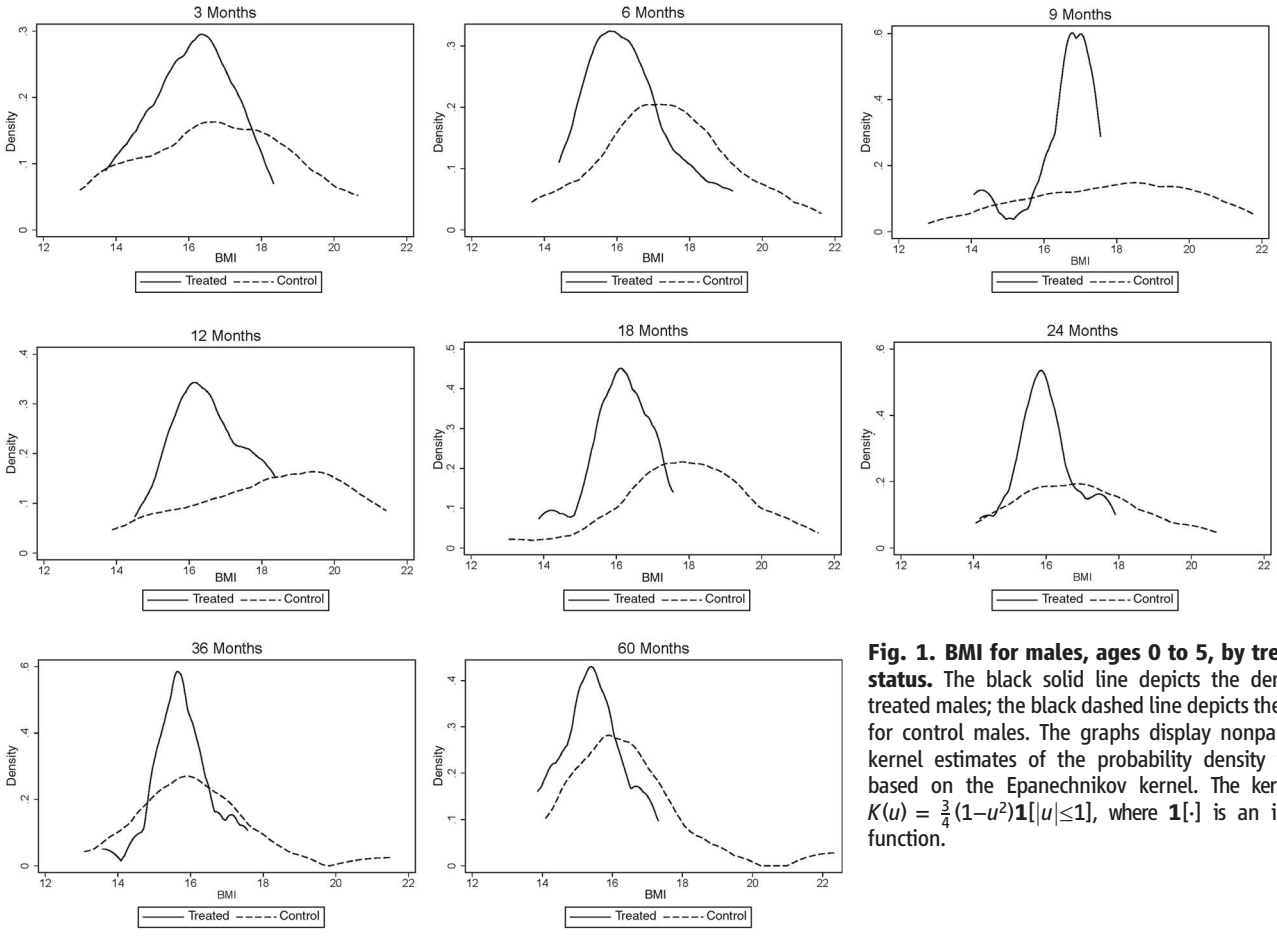

Fig. 1. BMI for males, ages 0 to 5, by treatment status. The black solid line depicts the density for treated males; the black dashed line depicts the density for control males. The graphs display nonparametric kernel estimates of the probability density function based on the Epanechnikov kernel. The kernel K is $K(u) = \frac{3}{4}(1-u^2)\mathbf{1}[|u| \leq 1]$, where $\mathbf{1}[\cdot]$ is an indicator function.

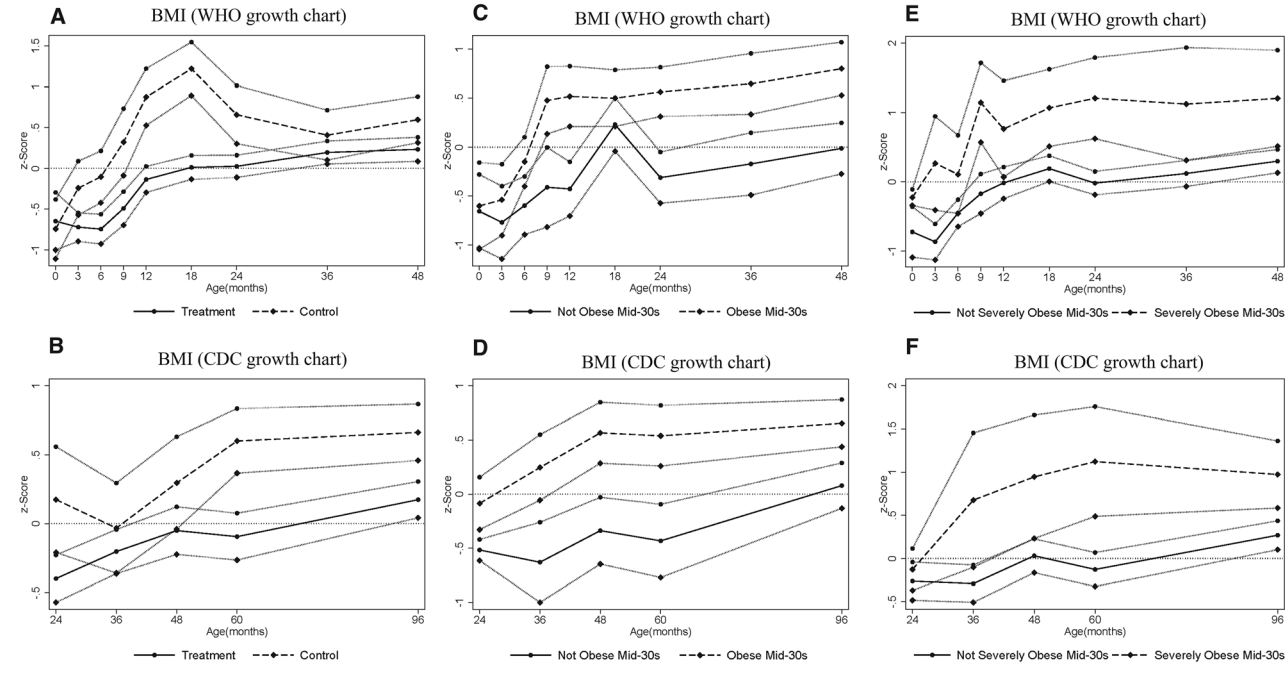

Fig. 2. BMI for males ages 0 to 4 years (A, C, and E) and 2 to 8 years (B, D, and F), by treatment and obesity status at mid-30s. The graphs show BMI z scores at different points in childhood (0, 3, 6, 9, 12, 18, 24, 36, 48, 60, and 96 months) by treatment and control status [(A) and (B)], by obesity status (BMI $\geq$ 30) in adulthood [(C) and (D)], and by severe obesity status (BMI $\geq$ 35) in adulthood [(E) and (F)]. Solid and dashed lines represent mean BMI by age for different groups, and the bands around each line represent standard errors for the corresponding means (one standard error above and below). (A), (C), and (E) use the WHO growth charts to construct the z scores; (B), (D), and (F) use the CDC growth charts. The CDC recommends the use of the WHO growth charts for less than 2 years of age (see www.cdc.gov/growthcharts/who_charts.htm).

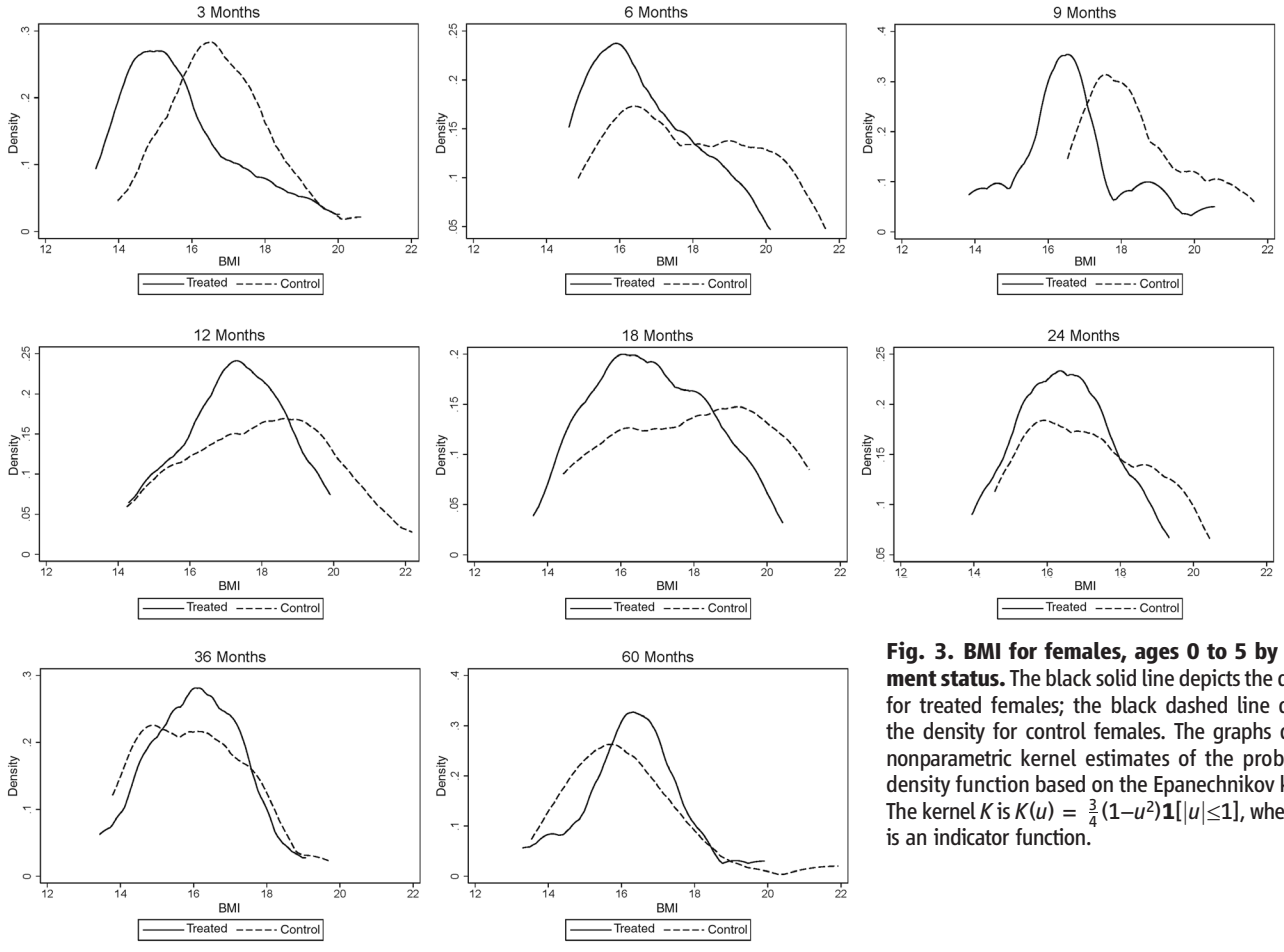

Fig. 3. BMI for females, ages 0 to 5 by treatment status. The black solid line depicts the density for treated females; the black dashed line depicts the density for control females. The graphs display nonparametric kernel estimates of the probability density function based on the Epanechnikov kernel. The kernel K is $K(u) = \frac{3}{4}(1-u^2)\mathbf{1}[|u| \leq 1]$, where $\mathbf{1}[\cdot]$ is an indicator function.

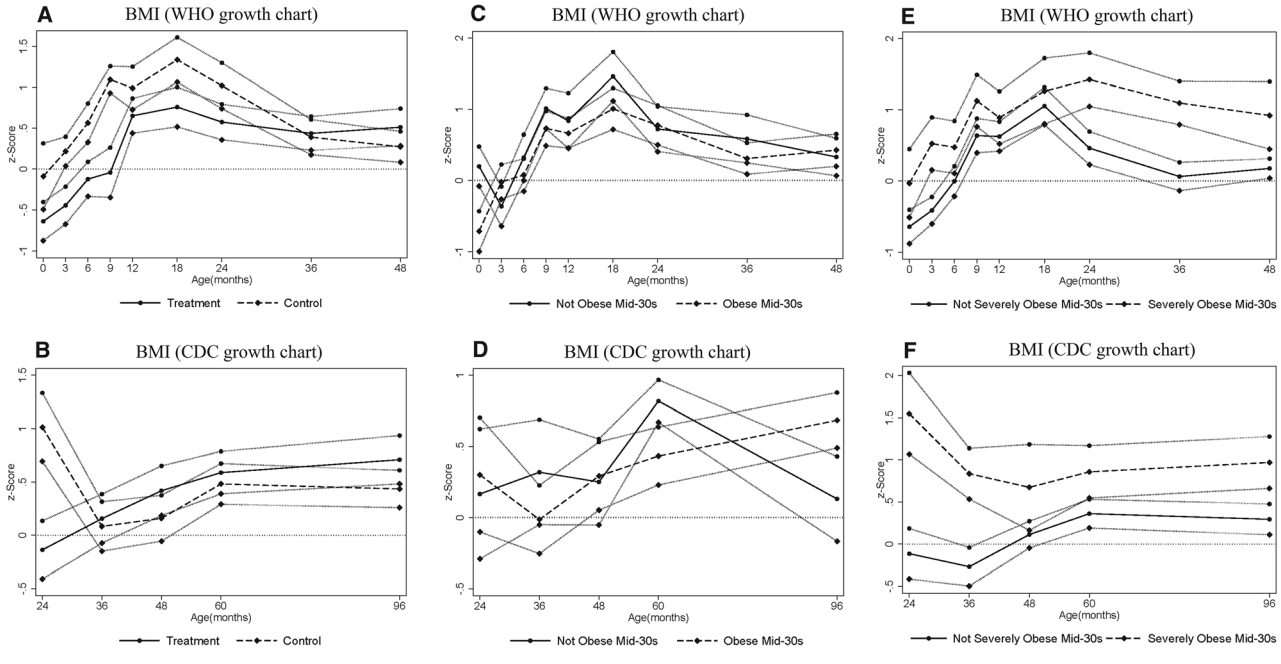

Fig. 4. BMI for females ages 0 to 4 years (A, C, and E) and 2 to 8 years (B, D, and F), by treatment and obesity status at mid-30s. The graphs show BMI z scores at different points in childhood (0, 3, 6, 9, 12, 18, 24, 36, 48, 60, and 96 months) by treatment and control status [(A) and (B)], by obesity status (BMI $\geq$ 30) in adulthood [(C) and (D)], and by severe obesity status (BMI $\geq$ 35) in adulthood [(E) and (F)]. Solid and dashed lines represent mean BMI by age for different groups, and the bands around each line represent standard errors for the corresponding means (one standard error above and below). (A), (C), and (E) use the WHO growth charts to construct the z scores; (B), (D), and (F) use the CDC growth charts. The CDC recommends the use of the WHO growth charts for less than 2 years of age (see www.cdc.gov/growthcharts/who_charts.htm).

Table 4. ABC intervention, females: health care at age 30; physical development in childhood. This table presents the inference and descriptive statistics of selected outcomes of the ABC intervention. The first column describes the outcome analyzed. The remaining six columns present the statistical analysis. The columns present the following information: (i) Control mean. (ii) Treatment mean. (iii) Unconditional difference in means across treatment and control groups. We multiply the difference in means by (−1) when a higher value of the variable in the raw data represents a worse outcome so that all outcomes are normalized in a favorable direction (but are not restricted to be positive). (iv) Conditional treatment effect controlling for cohort, number of siblings, mother's IQ, and high-risk index at birth, and accounting for attrition using IPW. The selection of covariates for IPW is based on the lowest AIC among models examining all combinations of covariates that present statistically significant imbalance between attriters and nonattriters. See supplementary materials section C and table S2. (v) One-sided single-hypothesis block permutation *P* value associated with the IPW treatment effect estimate. By block permutation, we mean that permutations are done within strata defined by the preprogram variables used in the randomization protocol: cohort, gender, number of siblings, mother's IQ, and high-risk index. (vi) Multiple hypothesis stepdown *P* values associated with (v). The multiple hypothesis testing is applied to blocks of outcomes. Blocks of variables that are tested jointly using the stepdown algorithm are delineated by horizontal lines. *P* values ≤ 0.10 are in bold type. We use weight-for-length $\leq$ 85th percentile for being "at-risk overweight" under 24 months, and BMI-for-age $\geq$ 85th percentile for being overweight for 24 months and older (*45*). See table S14 for complete estimation results.

Variable	Control mean	Treatment mean	Difference in means	Conditional treatment effect	Block *P* value	Stepdown *P* value
Health care at age 30						
Health insurance coverage at age 30	0.857	0.760	−0.097	−0.159	0.943	0.943
Buys health insurance at age 30	0.357	0.400	0.043	−0.027	0.511	0.810
Hospital or doctor office care when sick at age 30	0.929	0.800	−0.129	−0.131	0.875	0.964
Physical development in childhood						
At risk overweight (CDC) at 3 months	0.192	0.190	0.002	−0.036	0.418	0.757
At risk overweight (CDC) at 6 months	0.423	0.167	0.256	0.212	**0.040**	0.237
At risk overweight (CDC) at 9 months	0.360	0.143	0.217	0.181	0.169	0.548
At risk overweight (CDC) at 12 months	0.478	0.208	0.270	0.141	**0.055**	0.276
At risk overweight (CDC) at 18 months	0.440	0.318	0.122	0.118	0.311	0.669
Overweight (CDC) at 24 months	0.412	0.174	0.238	0.195	0.143	0.517
Overweight (CDC) at 36 months	0.261	0.143	0.118	−0.020	0.202	0.556
Overweight (CDC) at 48 months	0.192	0.409	−0.217	−0.247	0.944	0.944
Overweight (CDC) at 60 months	0.261	0.273	−0.012	−0.050	0.554	0.781
Overweight (CDC) at 96 months	0.174	0.350	−0.176	−0.230	0.943	0.985
Weight-for-length change 0–24 months (CDC)	0.857	0.918	−0.062	−0.052	0.658	0.688
Weight-for-length change 0–24 months (WHO)	1.129	1.215	−0.085	−0.006	0.660	0.660

importance of these early growth patterns is shown in Fig. 2. Fig. 2, A and B, shows the evolution of BMI-for-age during childhood for males by treatment status. It is noticeable that, while the BMI-for-age of the treatment group is always centered around the median for the reference population, the control group experiences a surge in the first year, which peaks at 18 months, becomes partially attenuated, and then exhibits diverging growth patterns after 5 years of age. It is striking that, when we consider the early growth trajectory by obesity status in adulthood (Fig. 2, C to F), those who are obese or severely obese in their mid-30s are already on a trajectory of above-normal BMI in the first 5 years of their lives. The effects of the intervention on early physical development are less pronounced for females (lower panel of Table 4 and Figs. 3 and 4). Fig. 4A and Table 4 show that there are significant differences in mean BMI-for-age and in the prevalence of being overweight, respectively, in the first 2 years of the intervention. These differences, however, fade out by the end of the daycare treatment. As observed for males, the females who are severely obese in their mid-30s are already on a trajectory of higher BMI-for-age in the first years of their lives (Fig. 4, E and F).

Conclusions

This paper analyzes recently collected biomedical data for the ABC intervention. Children randomly assigned to the treatment group for ages 0 to 5 have a significantly lower prevalence of risk factors for cardiovascular and metabolic diseases in their mid-30s. Treated males have a healthier body mass in their childhood years. These early benefits persist into adulthood.

The precise mechanisms through which these effects are obtained remain to be determined. It may be improved health due to access to pediatric care and proper nutrition in the early years, improved noncognitive skills as in the Perry study (*50*), improved cognitive skills, or some combination of all three factors. The bundled nature of the treatment does not provide the necessary independent variation in the components of the intervention that would allow us to examine the sources of treatment effects. A simple mediation analysis (presented in tables S19 and S20) suggests that half of the effect of the treatment on hypertension and obesity in the mid-30s may be mediated by the BMI of the child around 1 year of age, while no statistically significant role seems to be played by the availability of health insurance or improved socioeconomic status at age 30. However, the estimated mediation effects are not precisely determined, so these findings are necessarily speculative. Whatever the channel, our evidence supports the importance of intervening in the first years of life and suggests that early childhood programs can make a substantial contribution to improving the health of adult Americans and reducing the burden of health care costs. An intervention that lasted 5 years and cost $67,000 [in 2002 dollars (*51*)] produced sustained and substantial health benefits. Early childhood interventions are an unexplored and promising new avenue of health policy.

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44. The LMS method is an age- and gender-dependent transformation that translates BMI measures into *z* scores. The transformation is applied to two widely used population-based reference data: (i) the 2000 CDC growth standards; and (ii) the 2006 WHO child growth standards scale. The LMS method transforms the information on the median (M), coefficient of variation (S), and skewness (L) of the BMI distribution of these population-based reference data into a Box-Cox power function. This information is then used to transform BMI measures into *z* scores.
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49. A reduction in BMI can be caused by either better nutrition and/or more physical exercise. Physical environment is certainly important: the Frank Porter Graham (FPG) Child Development Institute included a large open space, and outside play was a part of the daily routine (11:30 am and 3:00 pm); however, this is likely to have played an important role only after the toddlers had started walking. Of course, better nutrition does not necessarily come only in the daycare center: The treated children could have enjoyed more nutritious food at home as well, both because their preferences for food might have been affected and because their parents were counseled by the pediatricians on site during the physical exams. Finally, (*47*) provides evidence—based on the What We Eat in America 2003–2004, combined with the National Health and Nutrition Examination Survey (NHANES) 2003–2004—that Head Start participants consume similar level of calories as non–Head Start participants during evenings and weekends but fewer calories in the morning and in the afternoon during the week.
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Supplementary Materials

www.sciencemag.org/content/343/6178/1478/suppl/DC1
Materials and Methods
Supplementary Text
Tables S1 to S26
References (*52*–*112*)

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Structure of the Yeast Mitochondrial Large Ribosomal Subunit

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Mitochondria have specialized ribosomes that have diverged from their bacterial and cytoplasmic counterparts. We have solved the structure of the yeast mitoribosomal large subunit using single-particle cryo–electron microscopy. The resolution of 3.2 angstroms enabled a nearly complete atomic model to be built de novo and refined, including 39 proteins, 13 of which are unique to mitochondria, as well as expansion segments of mitoribosomal RNA. The structure reveals a new exit tunnel path and architecture, unique elements of the E site, and a putative membrane docking site.

Mitochondria are organelles in eukaryotic cells that play a major role in metabolism, especially the synthesis of adenosine triphosphate (ATP). During evolution, mitochondria have lost or transferred most of their genes to the nuclei, substantially reducing the size of their genome (*1*). In yeast, all but one of the few remaining protein-coding genes encode subunits of respiratory chain complexes, whose synthesis involves insertion into the inner mitochondrial membrane along with incorporation of prosthetic groups (*2*). For the translation of these genes, mitochondria maintain their own ribosomes (mitoribosomes) and translation system. The mitochondrial ribosomal RNA (rRNA) and several transfer RNAs (tRNAs) are encoded by the mitochondrial genome, whereas all but one of its ribosomal proteins are nuclear-encoded and imported from the cytoplasm. Mitoribosomes have diverged greatly from their counterparts in the cytosol of bacterial and eukaryotic cells and also exhibit high variability depending on species (table S1) (*3*). Several genetic diseases map to mitoribosomes (*4*). In addition, the toxicity of many ribosomal antibiotics, in particular aminoglycosides, is thought to be due to their interaction with the mitoribosome (*5*).

Mitochondrial translation in the yeast *Saccharomyces cerevisiae* (*6*) has been used as a model to study human mitochondrial diseases (*7*). The 74*S* yeast mitoribosome has an overall molecular weight of 3 MD, some 30% greater than that of its bacterial counterpart. It consists of a 54*S* large subunit (1.9 MD) and a 37*S* small subunit (1.1 MD).

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