BLOOD GROUPS, SERUM CHOLESTEROL, SERUM URIC ACID, BLOOD PRESSURE, AND OBESITY IN ADOLESCENTS

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To assess the association of blood groups with coronary risk factors, data were examined from the third cycle of the National Health Examination Survey. In a nationwide sample of more than 6000 black and white adolescents aged 12 to 17 years, ABO blood group, haptoglobin phenotype, selected other genetic markers of blood and secretions, and coronary risk factor levels were measured. Blood group A_1 was associated with significantly higher serum total cholesterol levels in white females independent of multiple potential confounders, in white males independent of age and weight, and in southern black females independent of age and weight. ABO blood group was not significantly associated with blood pressure, resting heart rate, or subscapular skinfold thickness. An association with serum uric acid in white males was not independent of weight. In white males only, haptoglobin phenotype 2-2 was associated with significantly higher serum cholesterol levels than 1-1 or 2-1 adjusting for age and weight. No consistent associations were found between Rh types, ABH secretor ability, or group-specific component types and risk factors. This analysis of national data confirms previously reported associations of blood group A with higher serum total cholesterol levels in white adults and adolescents. (*J Natl Med Assoc.* 1991;83:682-688.)

Key words • ABO blood-group system • RH-HR blood-group system • secretor status • hyperlipidemia • uric acid

Several reports have suggested that ABO blood group A_1 is a marker for increased coronary heart disease risk,[1-5] possibly due in part to associations with increased serum cholesterol and blood pressure.[5-10] However, the independent association of blood groups with these risk factors is not well-established. This article examines the association of ABO blood groups with coronary heart disease risk factors in a large sample of US youths.

METHODS

The third cycle of the Health Examination Survey (HES) was conducted on a nationwide multistage probability sample of 7514 youths from the noninstitutionalized population of the United States aged 12 to 17

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years. This survey started in March 1966 and ran until March 1970. Out of 7514 youths selected for the sample, 6768 (90%) were examined. There were 5735 whites, 999 blacks, and 34 others. This article will be limited to whites and blacks. Details of the plan, sampling, response, and operation were published previously, as were procedures for obtaining informed consent and maintaining confidentiality of data.[11]

Demographic, medical history, and behavioral information were collected by household interview and self-administered questionnaires prior to the examination.[11] Conducted in a mobile center, the examination included a pediatrician's assessment of breast development stage in girls, male genital development stage in boys, and pubic hair stage in both sexes.[12]

Supine blood pressure at the beginning and the end of the physician's examination were measured by a nurse using a mercury sphygmomanometer as described in detail elsewhere.[13] The average of these two readings is used in the present analysis. Diastolic pressure was defined as the complete cessation of sounds. If sounds failed to disappear, the pressure at which muffling occurred was used. A pediatric or adult cuff was used as appropriate. Heart rate was measured from an electrocardiogram monitor strip containing 15 to 20 clear complexes taken with the subject standing quietly prior to a 5-minute treadmill exercise test.[11]

Blood samples were taken and sent to the laboratories of the Center for Communicable Diseases in Atlanta, Georgia for analyses of levels of total serum cholesterol by the Abell-Kendall method and serum uric acid by the Technicon Autoanalyzer I (Technicon Instruments Corp, Tarrytown, New York) (N-136 method), a calorimetric phosphotungstate procedure.[14,15] Whole blood for the genetic marker determinations was collected in a 15-mL vacutainer containing 2 mL of ACD Solution A to prevent coagulation and then refrigerated. ABO and Rh types were determined by standard saline tube agglutination with licensed blood-banding reagents.[16] Reverse grouping using the subject's plasma and known group A and B red cells was performed to confirm ABO typing. Haptoglobin, transferrin, and group specific component groups were typed after vertical polyacrylamide gel electrophoresis.[16]

For ABH secretor testing, at least 2 mL of saliva were collected immediately after the dental examinations from all subjects who did not have actively bleeding gums. After the addition of .05 mL of aqueous 4% thimerosal as a preservative, the sample was frozen at −20°C. Before testing, the samples were thawed, boiled for 10 minutes, and centrifuged. The clear supernatant was tested for A, B, or H substance by a semiquantitative agglutination inhibition test.[16] Details of laboratory procedures used for determining genetic markers have been described elsewhere.[16] The weighted frequency distributions of genetic markers by race, sex, age, geographic region, family income, and education of parent also have been published elsewhere.[16]

Technicians took an x-ray of the hand and wrist for assessment of bone age, and measured weight to the nearest pound, standing height to the nearest centimeter, and subscapular skinfold thickness to the nearest millimeter.[11,17] Prior to examination, body temperature was measured to the nearest .1°F with an oral thermometer; any subject with a temperature of 100° F or higher could be sent home and rescheduled for another date at the physician's discretion.

Population estimates for most of the variables have been published by the National Center for Health Statistics in the form of Series 11 reports.[13-17] Data in this article are not weighted to give precise estimates for the US population. However, the sample is large and similar to the general population in most demographic characteristics.[11] All descriptive statistics were computed by standard methods using unweighted data. Analysis of covariance was used to compute adjusted means for subjects within each blood group and to assess the statistical significance of differences in means among groups.[18] Covariance analysis tests for differences in intercepts assuming a constant regression relationship among groups. A test for heterogeneity slopes was performed to test the validity of this assumption by testing whether the regression coefficients were constant over groups.[18] Pairwise tests of least square means were used to assess probabilities associated with preplanned comparisons.

RESULTS

ABO Blood Groups

Cholesterol. Table 1 shows age-adjusted mean levels of serum cholesterol by ABO blood group. Age-adjusted mean serum cholesterol differed significantly among ABO blood groups for white males, $P = .05$. Group A_1 was significantly higher than group O ($P = .005$) *or group B* ($P = .04$). There was no significant interaction between ABO and age. These significant differences persisted after the control of weight and age or height, weight, and age. The overall differences were no longer significant after control of skeletal age alone or in addition to age and weight ($P = .09$), although specific contrasts of A_1 versus O ($P = .01$) and B ($P = .04$) remained significant. The

TABLE 1. AGE-ADJUSTED MEAN LEVELS OF SERUM CHOLESTEROL AND URIC ACID BY ABO BLOOD GROUP

	White Males		Black Males		White Females		Black Females	
	n	Mean ± SE	*n*	Mean ± SE	*n*	Mean ± SE	*n*	Mean ± SE
Serum Cholesterol (mg/dL)								
O	1358	170.7 ± 0.8	217	180.0 ± 2.3	1162	176.1 ± 0.9	234	180.8 ± 2.1
A_1	1009	174.2 ± 0.9	109	181.1 ± 3.2	931	181.0 ± 1.0	116	184.5 ± 2.9
A_2	226	170.8 ± 2.0	19	177.3 ± 7.7	164	179.5 ± 2.4	16	181.6 ± 7.9
B	303	170.2 ± 1.7	103	180.0 ± 3.3	274	173.7 ± 1.8	110	174.4 ± 3.0
AB	110	170.9 ± 2.9	20	183.8 ± 7.5	91	182.7 ± 3.2	26	182.0 ± 6.2
Serum Uric Acid (mg/dL)								
O	1358	5.51 ± 0.03	217	4.80 ± 0.08	1162	4.66 ± 0.03	234	4.21 ± 0.06
A_1	1009	5.43 ± 0.04	109	4.85 ± 0.12	931	4.65 ± 0.04	116	4.02 ± 0.09
A_2	226	5.45 ± 0.08	19	5.12 ± 0.28	164	4.68 ± 0.08	16	4.25 ± 0.24
B	303	5.45 ± 0.07	103	4.76 ± 0.12	274	4.68 ± 0.06	110	4.10 ± 0.09
AB	110	5.22 ± 0.12	20	5.51 ± 0.27	91	4.59 ± 0.11	26	4.18 ± 0.19

adjusted means ± SE expressed as mg/dL were A_1 174.0 ± 0.9, O 171.1 ± 0.8, B 170.1 ± 1.7), A_2 170.6 ± 2.0, and AB 169.9 ± 2.8. The results were similar if subscapular skinfold was substituted for weight.

In neither the sexually mature (Stage V) nor the immature (Stages I-IV) stratum based on male genital development was ABO blood group significantly related to serum cholesterol independent of skeletal age, skinfold, and age. In the subgroup with cholesterol above the sex-race specific median, ABO blood group was not significantly related to serum cholesterol after adjustment for age, weight, and height, or age, weight, and skeletal age. In black males, a significant interaction of ABO and age ($P = .04$) in the analysis of covariance for heterogeneity of slopes was found; therefore, age-adjusted means should be viewed with caution. No significant variation in age-adjusted means or unadjusted means was seen. Examination of age-specific data revealed no consistent patterns for black males. Further, in the subgroup of 237 black males from the South, there was no significant ABO-age interaction and no significant variation of age-adjusted cholesterol by blood type. In addition, no significant association was detected in the subgroup with cholesterol above the median.

Age-adjusted mean serum cholesterol differed significantly among ABO blood groups in white females ($P = .0003$) (Table 1). Group A_1 was significantly higher than O ($P = .0003$) and B ($P = .0005$). There was no significant interaction between ABO and age. These significant differences persisted after adjustment for weight and age; height, weight, and age; and skeletal age, weight, and age ($P = .0001$). The means ± SE expressed as mg/dL were A_1 180.9 ± 1.0, O 175.9 ± 0.9, B 170.25 ± 1.9, A_2 178.2 ± 2.2, and AB 183.5 ± 3.2 after adjusting for skeletal age, weight, and age. The results were the same if subscapular skinfold was substituted for weight in the model. Neither exclusion of two girls with cholesterol greater than 350 mg/dL nor controlling family income affected the results.

In females with Stage I-IV breast development, the ABO group was not significantly associated with serum cholesterol independent of skinfold and age. However, in the sexually mature (Stage V breast development), the association was highly significant ($P = .0003$). In this group, the age-skinfold-adjusted means ± SE were A_1 183.8 ± 1.5, O 177.3 ± 1.4, B 172.8 ± 2.9, A_2 183.8 ± 1.5, and AB 189.2 ± 5.2. The association appeared to reside chiefly in the subgroup with serum cholesterol levels below the sex-race specific median. Among black females, unadjusted or age-adjusted serum cholesterol did not differ significantly among blood groups, although A_1 tended toward higher levels (Table 1).

Blood Pressure. Table 2 shows that age-adjusted mean systolic or diastolic blood pressure did not differ significantly among ABO blood groups in any sex/race group. A trend toward higher systolic blood pressure in group O compared with group B and AB, and higher diastolic blood pressures in groups O and B compared with A_1 and A_2 was seen in white males only. There was no significant interaction of age with blood group in the analysis of covariance. No significant variation among blood groups appeared after adjusting for weight in addition to age.

Uric Acid. Table 1 shows age-adjusted levels of

TABLE 2. AGE-ADJUSTED MEAN LEVELS OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE BY ABO BLOOD GROUP

	White Males		Black Males		White Females		Black Females	
	n	Mean ± SE	*n*	Mean ± SE	*n*	Mean ± SE	*n*	Mean ± SE
Systolic Blood Pressure (mm Hg)								
O	1358	132.4 ± 0.4	217	128.5 ± 0.9	1162	127.8 ± 0.4	234	125.6 ± 0.8
A_1	1009	131.9 ± 0.4	109	127.7 ± 1.2	931	128.2 ± 0.4	116	127 ± 1.1
A_2	226	132.3 ± 0.9	19	128.8 ± 2.9	164	127.3 ± 1.0	16	124.7 ± 3.0
B	303	130.7 ± 0.8	103	128.3 ± 1.2	274	128.5 ± 0.8	110	126.4 ± 1.2
AB	110	130.7 ± 1.3	20	123.4 ± 2.8	91	128.1 ± 1.3	26	125.6 ± 2.4
Diastolic Blood Pressure (mm Hg)								
O	1358	73.4 ± 0.2	217	74.8 ± 0.6	1162	73.2 ± 0.2	234	74.6 ± 0.6
A_1	1009	72.6 ± 0.3	109	74.2 ± 0.8	931	73.2 ± 0.3	116	74.4 ± 0.8
A_2	226	72.4 ± 0.6	19	75.2 ± 2.0	164	73.9 ± 0.7	16	71.7 ± 2.2
B	303	73.7 ± 0.5	103	74.9 ± 0.9	274	73.7 ± 0.5	110	73.8 ± 0.8
AB	110	73.1 ± 0.8	20	73.3 ± 2.0	91	73.8 ± 0.9	26	72.6 ± 1.7

TABLE 3. AGE-ADJUSTED MEAN LEVELS OF HEART RATE AND SUBSCAPULAR SKINFOLD THICKNESS

	White Males		Black Males		White Females		Black Females	
	n	Mean ± SE	*n*	Mean ± SE	*n*	Mean ± SE	*n*	Mean ± SE
Heart Rate* (Beats/Minute)								
O	1284	85.9 ± 0.4	208	78.8 ± 0.9	1088	97.0 ± 0.5	209	87.9 ± 1.2
A_1	949	85.9 ± 0.5	102	76.8 ± 1.3	861	97.6 ± 0.6	105	87.4 ± 1.6
A_2	220	88.2 ± 1.0	18	75.1 ± 3.2	154	96.3 ± 1.4	14	85.0 ± 4.4
B	290	86.1 ± 0.9	99	76.2 ± 1.4	250	98.4 ± 1.1	96	88.7 ± 1.7
AB	107	84.4 ± 1.5	19	77.9 ± 3.1	85	99.8 ± 1.9	26	85.5 ± 3.3
Subscapular Skinfold Thickness (mm)								
O	1358	8.5 ± 0.2	217	7.4 ± 0.3	1162	11.9 ± 0.2	234	12.0 ± 0.5
A_1	1009	8.5 ± 0.2	109	6.7 ± 0.4	931	11.5 ± 0.2	116	11.3 ± 0.6
A_2	226	8.0 ± 0.4	19	7.7 ± 1.0	164	11.9 ± 0.6	16	13.2 ± 1.7
B	303	8.2 ± 0.3	103	7.5 ± 0.4	274	12.0 ± 0.4	110	11.3 ± 0.7
AB	110	8.9 ± 0.5	20	6.5 ± 1.0	91	11.4 ± 0.7	26	10.7 ± 1.4

*Numbers (*n*) for heart rate are slightly smaller due to missing data for this variable, for which no missing values were imputed.

serum uric acid by ABO blood group. Age-adjusted serum uric acid differed significantly among blood groups in white males ($P = .0001$). However, a significant age-by-ABO blood-group interaction was observed ($P = .03$); therefore, adjusted means must be viewed with caution. Serum uric acid was significantly lower in group AB than in group O ($P = .02$). Examination of age-specific data revealed lower serum uric acid levels in group AB at ages 12 through 16 but not at age 17 when group AB had the highest level of serum uric acid (group AB 6.17 ± 0.22; group O 5.93 ± 0.19). The overall difference in white males was no longer significant after controlling for weight and age ($P = .07$) although the AB versus O contrast remained significant ($P = .008$). Among black males, there was no significant difference among blood groups and no significant interaction with age. Age-adjusted serum uric acid did not differ significantly among blood groups in either white or black females.

Resting heart rate did not differ among ABO blood groups for any sex/race group (Table 3). An interaction in the model was observed for black males, but no consistent pattern could be detected in the age-specific data. The negative results persisted after adjusting for weight and age. Subscapular skinfold thickness did not significantly differ among blood groups for any sex/race group after adjustment for age (Table 3). Height was also unrelated to ABO after adjustment for age.

TABLE 4. AGE-ADJUSTED MEAN LEVELS OF SERUM CHOLESTEROL BY HAPTOGLOBIN PHENOTYPE

Phenotype	Males Mean ± SE	Females Mean ± SE
Whites		
Hp 1-1	169.0 ± 1.3	176.3 ± 1.5
Hp 2-1	171.1 ± 0.8	178.2 ± 0.9
Hp 2-2	174.4 ± 1.0	178.4 ± 1.0
Blacks		
Hp 1-1	177.8 ± 2.6	180.9 ± 2.6
Hp 2-1	182.0 ± 2.6	179.6 ± 2.2
Hp 2-2	182.9 ± 4.6	180.2 ± 3.5

Other Genetic Markers

No consistent patterns of risk factor differences among Rh types were observed in the four sex/race groups. ABH secretor ability also was not consistently related to risk factors. For example, in 12- to 14-year-old whites, mean ± SE serum cholesterol was 175.1 ± 0.9 in secretor and 175.0 ± 1.5 in nonsecretor boys and 178.0 ± 0.9 in secretor and 175.3 ± 1.7 in nonsecretor girls. In 15- to 17-year-old whites, corresponding means were 168.0 ± 0.9 versus 169.1 ± 1.8 in males and 179.1 ± 1.0 versus 178.5 ± 1.7 in girls. No significant interaction was found of secretor status with ABO blood group with respect to serum cholesterol in white males or females. No consistent patterns of risk factor differences were observed among group-specific component types. There were insufficient numbers of subjects with transferrin phenotypes other than CC to permit assessment of risk factor variation.

Haptoglobin. Table 4 shows age-adjusted mean ± SE serum cholesterol (mg/dL) by haptoglobin phenotype. Adjusted mean cholesterol was significantly higher in phenotype 2-2 ($P = .002$) in white males. No other significant associations were seen. The association for white males remained significant after adjusting for weight in addition to age.

Table 5 shows age-specific mean blood pressures in blacks. The apparent trend toward higher systolic blood pressures in black females with phenotype 2-2 was not significant after adjusting for age and weight. No significant associations were seen in other sex/race groups. Subscapular skinfold thickness showed no consistent association with haptoglobin phenotype across age, sex, and race groups.

TABLE 5. MEAN LEVELS OF BLOOD PRESSURE BY HAPTOGLOBIN PHENOTYPE IN BLACKS

Phenotype	Males Mean ± SE	Females Mean ± SE
Systolic: 12 to 14 Years Old		
Hp 1-1	124.0 ± 1.3	125.5 ± 1.4
Hp 2-1	126.4 ± 1.6	125.1 ± 1.1
Hp 2-2	122.3 ± 2.6	124.4 ± 1.8
Other	121.5 ± 1.7	128.6 ± 3.0
Systolic: 15 to 17 Years Old		
Hp 1-1	132.7 ± 1.7	128.2 ± 1.6
Hp 2-1	134.0 ± 1.3	127.2 ± 1.1
Hp 2-2	136.5 ± 2.6	125.6 ± 2.2
Other	128.3 ± 1.7	127.1 ± 2.9
Diastolic: 12 to 14 Years Old		
Hp 1-1	72.2 ± 0.9	73.0 ± 1.0
Hp 2-1	73.9 ± 1.1	73.7 ± 0.8
Hp 2-2	71.8 ± 1.4	72.1 ± 1.1
Other	69.0 ± 1.1	74.4 ± 2.3
Diastolic: 15 to 17 Years Old		
Hp 1-1	77.4 ± 1.2	76.5 ± 1.2
Hp 2-1	78.8 ± 0.9	74.7 ± 0.8
Hp 2-2	78.3 ± 2.0	75.5 ± 1.3
Other	75.8 ± 1.1	73.8 ± 2.2

DISCUSSION

Serum cholesterol was significantly higher in adolescents with blood group A_1 than those with blood groups O or B independent of age and weight but not skeletal age in white males. In white female adolescents, serum cholesterol was significantly higher in individuals with blood group A_1 than those with groups O or B independent of age, weight, subscapular skinfold thickness, and skeletal age. The differences were relatively small (4 mg/dL to 9 mg/dL). Significant independent associations of ABO blood groups with serum cholesterol in blacks or with serum uric acid, blood pressure, heart rate, or subscapular skinfold thickness in any sex-race group were not observed. Serum cholesterol was highest for haptoglobin phenotype 2-2 in white boys. The Rh blood groups, ABH secretor ability and group-specific component types showed no consistent associations with coronary risk factors.

The mechanism of the association of ABO blood group A_1 with higher serum cholesterol levels is unknown. Possibilities include a pleiomorphic effect of blood group genes to determine both red blood cell antigens and some aspect of cholesterol metabolism. Another possibility is linkage, ie, the location of genes associated with some determinants of serum cholesterol level on chromosome 9, the site of ABO genes.[8] Genes

specifying familial hypercholesterolemia may be located on the same chromosome as the gene specifying the third component of complement (C3), but the chromosomal location of these loci is currently unknown.[19] Several apoprotein genes are located on chromosomes 11 and 19.[20] The distribution of serum cholesterol values in white males and females with blood group A_1 in the present study showed no obvious bimodality. No information on parental risk factor levels or blood type was available. An earlier hypothesis that the association might be related to intestinal fat absorption[7] was not supported by the findings in this study.

The association of ABO blood group A_1 with increased serum cholesterol in whites is consistent with several reports in adult populations.[5-10] In a sample of Bogalusa, Louisiana adolescents, serum total cholesterol was also higher in those with blood group A among whites but higher in those with blood group B in blacks independent of age, weight, and sex.[21,22] In whites, blood group A_2 exceeded A_1 in serum cholesterol contrary to HES data. Nor did the association reside in those with higher cholesterol values in HES as in Louisiana. The HES results for both races differ from those of an Evans County, Georgia study, which found nonsignificantly higher serum total cholesterol levels in group O white or black school children and adolescents.[23] A study of English adolescents found no association.[24] Associations with lipoproteins remain poorly established.[21-23] Reports on serum uric acid found similar trends as those in this study in Brazilian military recruits but not in US or Colombian military samples or Australian civilians.[25-27]

Published reports on blood groups and blood pressure are conflicting as to the existence and nature of an association. In Bogalusa, Louisiana adolescents with systolic blood pressures adjusted for age, height, and weight above the 85th percentile had a higher representation of A phenotypes and a lower representation of B phenotypes compared to those with lower blood pressures.[28] Adjusted systolic blood pressure levels were higher in individuals with phenotype A than other phenotypes. Consistent associations were not found for blacks or for diastolic blood pressure. One Brazilian study observed a trend toward higher diastolic blood pressure in group O subjects, similar to the present observations in white male adolescents.[29]

Other studies have reported higher blood pressure in group A_1 subjects[9] or no association of ABO blood group with blood pressure or hypertension prevalence.[5,30] Rh blood groups generally have not been found by others to be associated with coronary risk factors[6,9,10,29,30] or coronary heart disease.[1]

Hypertensive and normotensive adults with haptoglobin phenotype 1-1 were more likely to respond to saline infusion followed by a diuretic with a 10 mm Hg or more drop in mean arterial pressure (sodium sensitivity) in one study; persons with phenotype 2-2 were more likely to have a decline of less than 5 mm Hg (sodium resistance).[31] Further, among the families of identical twins, individuals with haptoglobin phenotype 1-1 had a mean systolic blood pressure 6 mm Hg higher in adults and 8 mm Hg higher in children and mean diastolic blood pressure 6 mm Hg higher in adults and children compared to persons with phenotype 2-2.[31] In an Australian adult sample, systolic blood pressure was highest for phenotype 1-1 followed by 2-2 and 2-1.[27] In Tecumseh, Michigan, serum cholesterol was highest in females with haptoglobin phenotype 2-2 and nonsecretors of each sex.[32] Differences with HES study findings may have resulted from differences in study design, population selected, measurement techniques, or analysis methods.

The nature of the measured variables eliminates some of the bias usually associated with cross-sectional studies. ABO blood group is present from gestation and is not likely to be known by adolescents or, if known, not likely to influence behavior related to serum cholesterol levels. The present study population was both large and representative of a national population. For whites, the statistical power to detect associations was high. Inconsistencies in blacks may, in part, be due to the small numbers sampled and resulting large standard errors. The association of ABO blood group with serum cholesterol in white females was highly significant even after control of potential confounders.

Further genetic and population research is needed to determine the nature of the association of ABO blood groups with serum cholesterol. Development of a better theoretical basis for such studies would aid this effort. This could be facilitated by the identification of the chromosomal locations of genes specifying control of lipid metabolism. Other genetic markers need to be identified. The study of restriction fragment length polymorphisms associated with dyslipidemia is a promising approach.[20] Studies of ABO blood groups would be of interest in familial hypercholesterolemia and other inherited disorders of lipoprotein metabolism for which the likely mode of transmission has been established.

Further studies also are needed in populations of all ages of haptoglobin phenotypes, lipids, and blood pressure, in view of conflicting findings to date. Planners of future population surveys of coronary risk

factors may wish to consider including genetic markers such as ABO blood groups and family history of premature coronary heart disease along with measurements of lipoprotein fractions, obesity, and dietary intake in an attempt to account for both genetic and environmental sources of variation in serum cholesterol. ABO blood groups should be related to the various lipoprotein fractions and to their response to dietary and pharmacologic intervention.

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