The Influence of Environment
on Severe Obesity

by

Maria Matthews Daines

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Abstract

The Influence of Environment on Severe Obesity

by Maria Matthews Daines

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Objective: Explore environmental influences associated with severe obesity in context of family aggregation for obesity.

Design: "Familial" families were required to have at least two severely obese (SO) (BMI of 35 kg/m^2 or greater) siblings with one normal weight (NW) (BMI of 27 kg/m^2 or less) sibling. "Nonfamilial" families were required to contain only one SO sibling with all other first degree relatives meeting NW criteria (BMI of 27 kg/m^2 or less), and at least two NW siblings.

Setting: Data collection occurred over 36-months (January 1994 through December 1996) at Cardiovascular Genetics, University of Utah.

Subjects: Ninety-two familial and 53 nonfamilial sibships

Main Outcome Measures: Anthropometrics, physiological and emotional well-being, dietary intake, and activity level

Statistical Analysis Performed: Repeated measures analysis of variance tested for differences between SO and NW participants. T-tests compared differences between familial and nonfamilial SO individuals and between familial and nonfamilial NW individuals. A t-test compared mean intrapair differences (MID) between SO and NW siblings in nonfamilial and familial pedigrees.

Results: BMI was 3 kg/m^2 greater in SO familial versus SO nonfamilial participants ($p<0.05$) and 3.2 kg/m^2 greater in familial NW versus nonfamilial NW participants ($p<0.05$). The SO subjects had higher percent fat and total caloric intake and lower weight-adjusted total caloric intake and activity calorie

expenditure (weight-adjusted) when compared to NW subjects. Mean environmental measures between SO and NW subjects and MID between familial and nonfamilial MO and NW sibs did not differ.

Conclusion: Comparative analysis of SO and NW siblings demonstrate severe obesity to be associated with lower levels of perceived physical and emotional well-being, nutrient intake and physical activity. Further, environmental influences (life quality, nutrient intake, and physical activity) between familial and nonfamilial severe obesity families were similar when comparing SO and NW as well as MID of SO-NW. These data suggest similar genetic, environmental and interactive factors to be operative in the development of severe obesity among familial and nonfamilial severe obesity families.

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CHAPTER 1: SPECIFIC AIMS

The **major objectives** of this study are:

(1) Explore the influence of environmental factors on morbid obesity(MO);

(2) Determine whether environmental factors are significantly associated with the familial aggregation of morbid obesity.

The following **aims** specifically address these objectives.

These specific aims were addressed using a study population of 92 familial and 53 nonfamilial MO families.

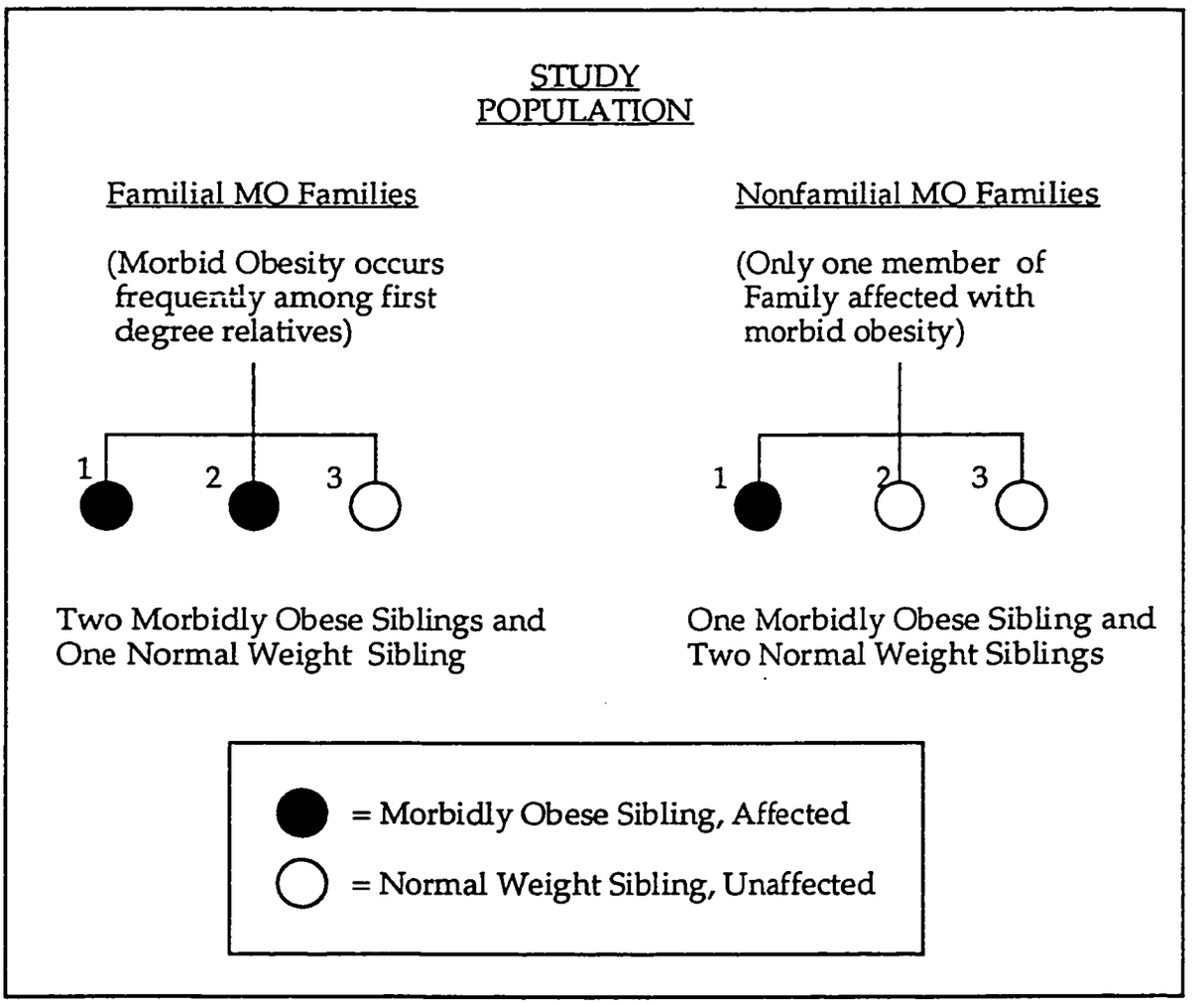

Figure 1: Study Population

Familial defined MO families were required to have within their family two morbidly obese siblings and one normal weight sibling. Nonfamilial defined MO families were required to have one and only one morbidly obese member amongst all normal weight first-degree relatives. In addition, the nonfamilial morbidly obese member needed at least two normal weight siblings. Environmental variables were compared between the three familial siblings (2 sibs morbidly obese; 1 sib normal weight) and the three nonfamilial siblings (1 sib morbidly obese; 2 sibs normal weight) (See Figure 1).

Using the strategy outlined in Figure One, the following questions with corresponding hypotheses have been developed.

Specific Aim-1

Do particular environmental factors differ significantly in morbidly obese (body mass index (kg/m^2)(BMI) > or = 35) and normal weight (BMI < or = 27) siblings?

Hypothesis: Environmental variables are associated with morbid obesity in familial and nonfamilial sibships.

Rationale: It is important to initially test whether environmental variables influence obesity in our study population before we delineate the familiality of environmental variables.

Specific Aim-2

How do environmental variables differ between familial and nonfamilial MO individuals?

Hypothesis: Since we assume that familial MO has a genetic basis, environmental factors should play a greater contributing role in nonfamilial (assumed less genetically influenced) MO than familial MO.

Rationale: We are uncertain if the same degree of environmental influences are required to maintain the obese status in familial MO versus nonfamilial MO.

Specific Aim-3

We will determine whether **mean intrapair differences** (MID) in environmental variables between affected (morbidly obese) and unaffected (normal weight) siblings differ in nonfamilial and familial pedigrees (See Figure 2).

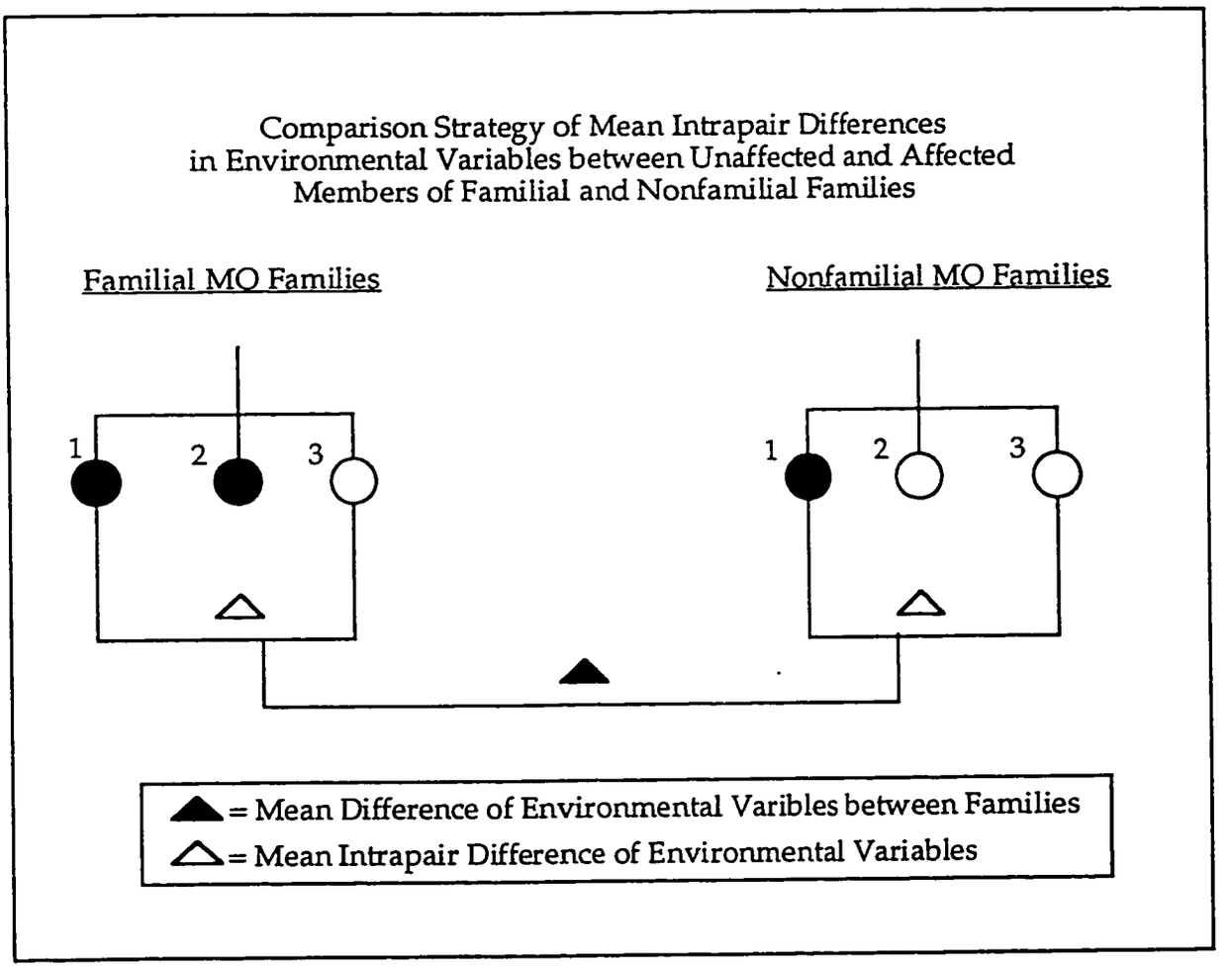

Figure 2: Comparison Strategy of Mean Intrapair Differences in Environmental Variables between Unaffected and Affected Members of Familial and Nonfamilial Families

Hypothesis : Since it is assumed that environment is responsible for the nonfamilial obesity, we expect to see greater differences in environmental factors between the nonfamilial unaffected and affected siblings than between the familial affected and unaffected siblings.

Rationale:

a. If we assume only gene carriers are affected in familial morbid obesity families, affected and unaffected siblings could potentially have the same environmental risk factor profile, yet only the gene carrier becomes obese. Thus, the unaffected sibling could have the same environmental risk factor profile (i.e., a small and nonsignificant MID), yet only the gene carrier becomes affected.

b. If MO is environmentally caused in nonfamilial morbid obesity families, the affected and unaffected sibling should have statistically different environmental risk factor profiles (a significantly different MID).

c. If these assumptions are true, we would hope to differentiate the extent of environmental influence contributing to MO in these two family types.

Considerations:

As this is a cross-sectional study, cause versus effect of MO (e.g., did the low activity level cause the obesity or develop as a result of being obese) cannot be determined. However, a cross-sectional study can generate hypotheses of association between environmental factors and MO which could be further explored in a prospective study design.

CHAPTER 2: BACKGROUND

The incidence of both obesity and overweight in the United States has increased strikingly over the past 30 years (142). While many health risk indicators such as blood pressure, blood cholesterol, coronary heart disease and stroke are declining in prevalence in the U.S., initial findings from NHANES III data (Phase 1:1988-1991) reveal that the prevalence of overweight (body mass index, BMI) has increased by 8 percent (6,42,78).

Although unclear what correlation might exist between significant increases in BMI and mortality/morbidity risk, there remains a certainty regarding the current major risk of morbid obesity on early disability and death. Morbidly obese men have a 12 times increased mortality rate when compared to normal weight men of similar age and morbidly obese women have a mortality rate of six times the normal weight female (21). In addition, morbid obesity significantly increases the risk for hypertension, diabetes, gallbladder disease, coronary artery disease, arthritis, operative risk and pulmonary dysfunction (7,87,78,128).

I. Genotype-Environment Interaction in the Development of Morbid Obesity

A. Genetics of Obesity

Obesity results from the combined effects of genetic and nongenetic factors, with the relative contributions of each being unclear.

1. Genetic Susceptibility

Obesity-related genes are best regarded as conferring susceptibility to obesity, rather than producing the phenotype per se. A susceptibility gene is defined as one that increases susceptibility or risk for the disease, but is not

necessary for disease expression. An allele (an alternative form of a gene at a particular locus) at a susceptibility gene may increase the likelihood of the carrier becoming obese, but the presence of that allele is not sufficient by itself to explain the occurrence of the disease. The alternative allele merely lowers the threshold for a person to develop the disease. In contrast, the evidence for the contribution of behavioral and lifestyle factors in the development and maintenance of obesity is abundant and generally strong. (These behavioral and lifestyle factors will be addressed in detail in later sections.) An analogy of this genetic/environment interaction suggests that genetics is the "cannon" and the environment is the "fuse." Thus, it is becoming increasingly recognized that there are inherited differences in the susceptibility to obesity under given behavioral and lifestyle conditions.

2. Genetic Heterogeneity

The development and clinical expression of obesity is so heterogeneous that it seems unlikely that all cases of obesity may be due to any one susceptibility gene. The number of separate mutants associated with obesity in other mammalian species also suggests heterogeneity. On the other hand, while polygenic factors are obviously important in obesity, the reviewed studies propose that not all relevant obesity genes fit the polygenic model, that is, have small additive effects (9). These studies suggest that extreme cases or morbid obesities may be influenced by a single gene. Thus, it is hypothesized that single genes with major effects may account for most cases of morbid obesity within individual families. Overall, it is likely that several major obesity genes and polygenes aggregate in particular families.

3. **Familiality of Obesity**

Analyzing our family data (see Methods section concerning our Family Health Tree program) indicate that morbid obesity occurs in less than 5% of the general population. In contrast, data from our entire cohort of morbid obesity families showed morbid obesity occurred in the family members of MO probands from 8 to 24 times more often than in the general population.

In 1993, our group reported strong familial aggregation of morbid obesity, with 48 percent of the morbidly obese probands having one or more first degree relatives who were also morbidly obese (1). Although this study showed 48 percent of the morbidly obese probands to have at least one other morbidly obese first degree relative, the remaining population of morbidly obese probands (52% of probands) were the only one among their first degree relatives who were morbidly obese. This finding initially suggested that among the nonfamilial morbidly obese subjects there may exist a strong environmental influence leading to severe obesity. However, in an article recently submitted for publication, we reported that families initially ascertained (through our family data base) as nonfamilial (a proband without any morbidly obese first degree relatives and without less severe forms of obesity) were frequently found to be familial (probands with at least one other morbidly obese first degree relative) after actual contact with family members was made. The nonfamilial morbid obesity families that ultimately qualified for the study and were actually ascertained for data acquisition represented only 8.1 percent of the total initial nonfamilial data pool. By comparison, the familial morbid obesity families who were ultimately ascertained for the study represented 81.9 percent of the initial familial data pool (Appendix 11).

4. **Segregation and Linkage Analysis**

Having verified the aggregation of morbid obesity within families, we tried to determine whether it resulted from genes, shared environment or both using segregation analysis. Analysis of all segregation models (environmental, mixed major-gene, dominant gene, and recessive gene models) were rejected compared to the general model. The rejection of the segregation models may be due to the fact that human obesity is a complex multifactorial condition evolving under the interactive influences of dozens of affecters from the social, behavioral, physiological, metabolic, cellular and molecular domains. Furthermore, segregation of genes is not easily detected in familial or pedigree studies, and whatever the influence of the genotype on the etiology it is generally attenuated or exacerbated by nongenetic factors.

The rejection also could have been due to genetic heterogeneity and/or strong temporal changes in the expression of the gene. For example, during the past half century, there have been large increases in the prevalence of obesity in developed countries. Such short-term changes in prevalence may be environmentally determined or the result of cultural changes. However, genes may mediate phenotypic response to environmental change, e.g. through variable gene penetrance and expression. The recent increases in obesity may incorrectly suggest a recessive pattern, since the prevalence of obesity is higher in offspring than in parents---as would be the case if most parents were normal-weight heterozygous carriers (95). Therefore, for humans it appears that genotype may determine the response to obesity-promoting environments.

We are currently looking for genes shared more commonly among affected family members than would be expected by chance. This involves the identification of candidate genes through familial linkage of random DNA markers with the obesity phenotype. A large number of these markers are highly

polymorphic or have substantial individual difference in DNA sequences. Nearly all parts of the human genome have markers spaced no more than 5 million base pairs apart, and many parts of the human genome are more densely mapped.

The closer together two loci lie on the same parental chromosome, the less often their alleles are separated as DNA is exchanged between homologous chromosomes during meiosis. One can gain a measure of the distance between a gene of particular interest and a marker by correlating the inheritance pattern of their alleles. If affected individuals always inherit the same version of the marker, the mutant gene and the marker must lie very close together on the same chromosome. The marker and the disease gene are said to be linked. Other markers lying farther from the disease gene will recombine with the gene more frequently.

Linkage analysis appears to be the most practical for identifying genes for obesity and other complex phenotypes because no specific model of inheritance is assumed. Additionally, the required genetic markers are available and these markers are highly polymorphic.

5. Candidate Obesity-Predisposing Genes

Another approach to mapping human obesity genes involves testing for linkage of obesity genes identified from other species in human obesity. For example, in 1995, mouse obese gene (OB) was identified and the protein product, leptin, encoded. Injection of leptin into obese mice resulted in weight loss and weight-loss maintenance. However, researchers have not found any mutations in human OB gene. In fact, adipose tissue of obese subjects overexpresses leptin protein. Several other candidate genes have been identified in animal models: fat gene (FAT), diabetes gene (DB) and uncoupling protein gene (UCP). The mouse FAT gene causes gradual obesity as mice age. The FAT gene encodes

carboxypeptidase E, an enzyme which cleaves hormonal precursor proteins (including proinsulin and neuropeptide Y) generating active hormones. The DB gene is believed to encode the leptin-protein receptor located in the ventromedial nucleus of the hypothalamus. If obese individuals produce enough leptin protein, perhaps the leptin protein is unable to bind to its receptor appropriately. The UCP gene encodes uncoupling protein, a mitochondrial protein that generates heat instead of ATP from the hydrolysis of fatty acids, expending instead of storing energy (5,26,27).

These candidate genes are just a few examples of the increasing number of candidate obesity genes. With the excitement of locating genes associated with obesity in animal models, it is important to note that none of these candidate obesity genes have been consistently validated in human obesity.

6. <u>Gene Environment Interaction</u>

Both genes and a shared environment can endow members of a family with a predisposition to obesity (70,140). The possible synergistic interaction between genetic and environmental factors can produce even more dramatic susceptibility to obesity than either factor alone or both added together (140).

To assess the relative roles of genes, the environment and their interactions, medical studies of twins, pedigrees and families with adopted children have been conducted. Griffiths and Payne (42) showed that normal weight children with obese and lean parents differ in their caloric intake, activity-related caloric expenditure and estimated resting metabolic rate. Hartz, et al., (45) reported that family environment accounted for 39% of the variation in obesity using subgroups of children similar with respect to sex and age. The estimate of heritability was quite low, only 11%. Garn, et al., (32) reported that adoptive parents and their adopted children tend to resemble each other in height, weight and fatfolds to an

extent paralleling height, weight and fatfold resemblances of biological parents and their children. Furthermore, Garn, et al., (34) showed that fatness increases in a stepwise fashion according to parental fatness combinations (Lean X Lean through Obese X Obese) for both biological and adopted children, indicating that fatness (while strongly familial) is not necessarily genetic. These results suggest that family environment, which consists of such things as energy intake, dietary habits, and learned patterns of energy expenditure and conservation, has an important effect on childhood obesity, and that many family-line resemblances are inflated by the results of living together (35).

In contrast, Stunkard, et al., (123) studied 540 adult Danish adoptees to assess the contribution of genetic factors and family environment to human fatness. Adoptees were divided into four reported weight classes as determined by BMI: thin, median weight, overweight and obese. Reported height and weight data were also collected from the adoptees' biologic and adoptive parents. Results showed a strong relationship between weight class of the adoptees and the BMI of their biologic parents: for the mothers, $p<.0001$ and for the fathers, $p<.02$ (one-way analysis of variance). No relation existed between the weight class of the adoptees and the BMI of the adoptive parents. Two recently reported twin studies, one involving long-term overfeeding and the other a BMI study of twins reared apart, have demonstrated weight gain, fat distribution and BMI are highly related to genetic influences (10,122). Bouchard (10) demonstrated that identical twins are very similar in amount of weight gain in response to overfeeding, and Stunkard (122) found that body fat is strongly influenced by genetic factors in twins reared apart (heritability of approximately 0.6; thus, about 60% of the variance in body fat may be accounted for by genes).

Some studies suggest genes determine who is susceptible to becoming obese and that environment determines the extent of obesity in vulnerable individuals.

For example, Price and Stunkard (89) found that the concordance for overweight was high but that the correlation between identical twins was significantly lower among pairs drawn from an overweight group than among pairs drawn from a normal weight group. Because morbid obesity most likely results from the accumulation of environmental factors over time in genetically susceptible persons, further inquiry to identify genetic and environmental parameters involved in the development of morbid obesity is essential.

B. Environment/Genetic Analysis

As previously concluded, the nature of environmental influences on individual differences in weight gain and obesity is presently unclear. Documentation of a major role for genetic factors in obesity does not rule out the importance of life experiences. If there are significant environmental influences on weight gain and obesity, it would be critical to understand these causes in order to elucidate methods of prevention or intervention.

In examining the role of environment in obesity, the two bodies of research that emerge are those where environmental experiences are shared among family members and those that are not. Examples of specific experiences that tend to be shared among family members include parental behavioral characteristics, some parental rearing practices, socioeconomic status, same family mealtime practices, and overall family emphasis on physical fitness. In contrast, nonshared environmental effects reflect the distinctly individual experiences that are not shared among family members. For example, the only reason that genetically identical monozygotic (MZ) twins who are reared together differ from each other is the effect of life experiences that they do not share. Examples of specific experiences that tend not to be shared among family members include perinatal insult, head injuries, accidents, some peer relationships, and differential rearing

practices (44).

1. Shared Environmental Experiences

The behavior/genetic analysis conducted by Grilo and associates (44) concluded that experiences shared among family members **do not** play an important role in determining individual differences in weight, fatness and obesity. They noted that monozygotic twins reared together, who share both 100% of their genes and their rearing environments, show no greater resemblance than did MZ twins reared apart, who share only their genes (88,122), and cohabitating spouses do not show increased resemblance for weight compared with engaged couples, who have not yet lived together (44). When Grilo et al. examined shared environments, it seems that currently living together is no more important than relatives who are no longer living together. For example, monozygotic twins under the age of 18 years old who have been reared together and are currently living together generally do not resemble each other more for weight than do older MZ twins who were reared together but are no longer living together (44).

2. Non-Shared Environmental Experiences

Upon reviewing the limited studies addressing non-shared environmental experiences, Grilo and colleagues (44) concluded that environmental experiences not shared among family members seem to constitute most of the environmental influence on weight and obesity. Discordance between MZ twins reared together is the most frequently used design to estimate the importance of nonshared environmental influences. As MZ twins share 100% of their genes and their rearing environments, any observed differences between them may be attributable to nonshared environmental experiences. Estimates that are based on MZ twins suggest that approximately 20% of total weight variation is due to environmental

experiences that are not shared between MZ twins, even those between younger twins who are likely to currently live together (44,121). As of yet, these non-shared environmental experiences have not been specifically identified and reported as influential on obesity.

II. Environmental Variables Influential in Weight Gain

To date, the few intervention studies in which environmental variables (primarily diet and exercise) have been altered in morbidly obese study groups have had poor results due to high frequency of relapse after weight loss (14,58,72,118). Using a subset of the population who are morbidly obese, this research will help us to understand the environmental characteristics associated with familial and nonfamilial obesity by measuring dietary intake, energy expenditure and other environmental factors believed to influence body weight or weight gain. Patterns of environmental risk factors in these two types of families may suggest specific intervention strategies.

A. Dietary Intake

The expression of obesity is modified by environmental influences such as caloric intake and energy expenditure, and this expression may depend further on the macronutrient composition of the habitual diet. Dietary factors clearly play a major role in the regulation of body weight. Given genetic predisposition, Stunkard suggests that the extent of obesity seems to be determined by long-term exposure to a given diet---either of excessive caloric intake or an altered macronutrient composition (119).

1. Macronutrient Composition

When considering the heterogeneity of human obesities, some obese

individuals may be more susceptible than others to the effects of diet. More specifically, it may be that a genetic predisposition to obesity is reflected in an increased vulnerability to dietary challenge. One type of challenge may involve the exposure to sweet or high-fat foods. Animal studies have shown that various strains of rats are differentially susceptible to the effects of sugar- or fat-supplemented diets (109). Osborne-Mendel rats are far more susceptible than the Sprague-Dawley strain to prolonged feeding with a high-fat diet (110). Similarly, increased appetite for sweet or high-fat foods may be one behavioral mechanism by which susceptible individuals gain body weight.

a. Fat Intake

Although human data are still limited, recent dietary intake studies suggest that the habitual diet of obese men and women may be rich in fat (69,102,127). The wide availability of high fat foods in the typical American diet may be an important risk factor, promoting the expression of obesity among susceptible individuals. Dietary intake studies have shown that obese women consumed more fat calories than did lean women and had a lower dietary carbohydrate:fat ratio (102). In taste preference studies with sugar/fat mixtures, obese women preferred sensory stimuli that were relatively low in sugar but high in fat (23). Dreon et al. reported that high levels of body fat were correlated with the amount of fat in the diet (22). Other investigators have confirmed that sensory preferences for a given level of fat in foods (not necessarily fat consumption, but percent of fat in individual food items) are linked to the subject's own percentage of body fat (74).

b. Fiber Intake

Cleave, Burkitt and Trowell used epidemiological observations to link low dietary fiber intakes to the occurrence of obesity and other diseases common in

Western society (16,18). Cleave suggested that most of the obesity prevalent in industrialized society is due to replacement of crude carbohydrate by refined, low fiber foods.

Lovejoy and DiGirolamo reported that obese subjects consumed significantly less fiber and carbohydrate than did lean subjects (71). These researchers also found a significantly higher fat and lower carbohydrate intake in obese subjects than in lean subjects. Alfieri, et al, also reported a lower fiber intake in their obese participants than in the lean participants (2). Lastly, several studies have shown that fiber supplements successfully aid in weight loss in overweight persons (97,115,132).

2. Caloric Intake

Excess storage of energy in adipose tissue results from an imbalance of food intake and caloric expenditure. However, most available studies of energy intake have shown that obese subjects do not eat more than their non-obese counterparts (4,38,62,93). Nevertheless, the theory---supported by research conducted by Lansky and Brownell---that excessive food intake is the cause of obesity is still largely accepted (38). Lansky and Brownell found that obese patients under reported daily caloric intakes by one-third or more (64). Furthermore, acquiring accurate dietary intake data from obese patients is notoriously difficult (23).

Interestingly, analysis of the NHANES I data, which were based on 24-hr food recalls, found a negative correlation between overeating and overweight (11). The most obese women appeared to be consuming the fewest calories. Furthermore, Kromhout reported greater obesity was associated with lower caloric intake in obese men (62). One study, however, conducted with a large patient population in a Paris hospital, did demonstrate a positive relationship between BMI (body mass index) and dietary intake (31).

Thus, data are inconclusive regarding overeating and excessive caloric intake, but suggest that their diet may be rich in fat.

3. Genetic versus Cultural Inheritance of Food Intake

Considering the genetics of dietary intake, a recent study by Perusse, et al. (86), reported that after examining 375 families no significant genetic effect was found for intake of any nutrient tested, and cultural inheritance was found to be more important than genetic inheritance. Their results suggest the average genetic influence on nutrient intake is negligible and that nongenetic effects associated mainly with home environment are the major affecters of energy intake.

Sellers, et al., (113) reported that dietary variables correlate between adult siblings even after they no longer live together in the same household. Sellers' data showed that dietary patterns among adult siblings living apart are more alike than could be predicted by their sharing a common culture, (as alike as has been described for monozygotic twins), (28,48,50,59,108) and sufficiently alike as to raise problems for any simple attribution of genetic explanations to the biologic characteristics of morbid obesity. This suggests shared dietary habits continue into older ages and that both current and past dietary intake may contribute to familial correlation of obesity.

Examining dietary intake for total calories, specific nutrients or their ratios to total calories, or familial variance of a similar nutrient intake may allow estimation of the relative importance of diet in morbid obesity, as well as prove to be statistically predictive of morbid obesity.

B. Energy Expenditure

While obesity results from a positive energy balance with caloric intake

exceeding expenditure, research on caloric intake and expenditure suggests that obese and lean may not differ in intake, but rather differ in expenditure (20).

1. Reduced Physical Activity

Kromhout, et al., reported in the Zutphen study that physical activity per kilogram body weight was inversely related to indicators of body fatness (33). Furthermore, Ravussin, et al., showed that low rates of energy expenditure were significant predictors of gains in body weight (93). Several studies have shown that obese children are less active than lean children (15,20,57). Epstein, et al., (24) reported a lower enjoyment rating of activities for offspring of obese parents in comparison to offspring of lean parents.

Roberts, et al., (100) investigated energy expenditure in infants born to lean and overweight mothers and found that neither reported energy intake or resting energy expenditure (REE) measured by indirect calorimetry differed significantly between the groups. However, the total energy expenditure (TEE) of infants who were becoming overweight was 20.7% lower, on average, than all normal infants combined. These findings indicate that at 3 months of age, low energy expenditure rather than high energy intake was the principle cause of rapid weight gain in the infants becoming overweight. In addition, the finding of no difference in REE between groups, despite a significant difference in TEE, supports the premise that the lower TEE in infants who were becoming overweight was due to reduced energy expenditure for physical activity and/or arousal.

Griffiths and Payne (42) measured TEE, REE, energy intake and body composition in 4 to 5 year old children of normal-weight parents and children of one normal and one obese parent. At the time of this study, there was no significant difference in body weight or composition between children of normal and obese parents. However, the children of the obese parent had a significantly

lower TEE and energy intake than the children of normal parents, by 22% on average---which is very similar to the TEE reduction found in the study conducted by Roberts. Interestingly, the children of the obese parents also had significantly lower values for REE. In contrast, in Roberts study the infants of the obese parents had no significant reduction in REE. The reduction in the Griffiths and Payne study accounted for approximately half of the reduction in TEE.

A recent follow-up investigation of the same population (studied by Griffiths and Payne (43)) at age 15 to 16 years showed that the children of the obese parents subsequently gained substantially more weight than the children of normal parents. These findings suggest that the low energy expenditure earlier in life did facilitate increased weight gain. In addition, it was also shown in this follow-up study that REE remained depressed in children of an obese parent relative to that in children of normal-weight parents.

Roberts, et al (101), used the doubly labeled water method to measure TEE in young and elderly men. They demonstrated a negative association between the TEE/REE ratio (a measure of the energy expenditure for physical activity normalized for lean body mass) and the body fat content determined by underwater weighing. Rising, et al. (98), reported that obese Pima Indians are less active than their lean counterparts. Their results suggest that obesity is associated with lower levels of physical activity. (Furthermore, Chirico and Stunkard found that when physical activity was measured by pedometers and activity questionnaires, obese men and women were less active than their lean counterparts (17).)

Weinsier, et al. (137), conducted a prospective study in which 24 previously obese (post-obese) women were compared with 24 never-obese women of comparable age and body composition. At the beginning of the study, the following measured parameters in the post-obese women were similar to the

never-obese controls: mean resting energy expenditure, thermic effect of food, and fasting and postprandial substrate oxidation and insulin-glucose patterns. Four years later, without intervention, the women predisposed to obesity regained essentially all of their lost weight, whereas all of the never-obese women maintained a normal weight. Despite this difference, neither resting energy expenditure, the thermic effect of food, nor the patterns of fasting or postprandial fuel utilization were predictive of long-term weight gain in either group. Only the self-reported physical inactivity was associated with greater weight regain. Zurlo, et al. (144), reported that spontaneous physical activity, the name given to small 'fidgeting-type' movements, had significant interindividual variations of about 400-3,000 KJ/day (100-800 kcal/day) and that a low spontaneous physical activity was associated with subsequent weight gain in men. In a 2-year follow-up study of 45 previously obese subjects, Ewbank, et al. (25), demonstrated that high-activity patients maintained significantly greater weight loss and had a lower percent regain than less active patients.

2. Resting Energy Expenditure

Resting energy expenditure, even for persons with the same lean body mass, age and sex, may vary as much as 20%. Thus, if the mean resting expenditure is 1,000 kcal per day, two persons of normal weight could differ by 400 kcal per day (1,200 versus 800 kcal per day) (12). In a careful study of the resting metabolic rate among family members, Bogardus and colleagues (8) showed that metabolic rate clustered in families. If one person was below the median for energy use, other members of the family also tended to be below the median. They showed that resting metabolic rate is a familial trait that is independent of differences in fat-free body mass, age, and sex. Linear regression analysis indicated that 83% of the variance in resting metabolic rate was accounted for by the covariates of fat-

free mass, age and sex. When family membership was added to the regression model for predicting resting metabolic rate, 94% of the variability of the resting metabolic rate was explained. The mean resting metabolic rate among families varied by nearly 500 kcal per day, but the mean variation within families was only about 60 kcal per day (8). The aggregation of resting metabolic rate indicates a genetic influence. As resting metabolic rate aggregates in families, research has shown that genetic factors account for between 30% to 40% of the variance in resting metabolic rate after adjusting for age, sex and body composition (96). The significance of a reduced metabolic rate to obesity was supported in a longitudinal study conducted by Bogardus and colleagues in which they found suggestive evidence that weight gain in relation to lean body mass is more likely in those with lower metabolic rates (93).

3. Energy Efficiency---A Risk for Obesity

Ravussin, et al. (93), conducted a longitudinal study in which indirect calorimetry was used to determine whether low rates of energy expenditure at rest for over a 24-hour period were associated with an increased risk of subsequent weight gain. They reported that low rates of energy expenditure, adjusted for fat-free body mass, fat mass, age and sex, were significant predictors of gains in body weight in a population prone to obesity. The adjusted 24-hour energy expenditure was inversely related to the amount or rate of change in body weight. This implies that subjects with similar physical characteristics can require more or less energy to maintain their body weights and can therefore be more or less "energy efficient." These data support the belief that there may be similar metabolic differences among humans and to hypothesize that people with lower rates of energy expenditure have a higher risk of weight gain. Leibel and Hirsch showed that formerly obese subjects needed 24 percent fewer calories per unit of body

surface area to maintain their new weights than control subjects (65). Geissler, et al. (39), observed in 16 formerly obese subjects that metabolic rate measured over 24-hours was about 15 percent lower than the rate of 16 matched lean controls.

These studies indicate low energy expenditure facilitates weight gain in genetically susceptible individuals. Furthermore, the observed steady-state between the level of energy expenditure for physical activity and body composition in weight stable subjects suggest that energy expenditure for physical activity may have a long-term effect on the level of body fat carried by an individual (101). Therefore, the relationship between physical activity and body fat content indicate that physical activity may indeed play an important, causal role in determining the body fat content of healthy adults.

C. Socioeconomic Conditions

In addition to diet-related and energy expenditure factors, other psychological and sociocultural variables may contribute in different ways to the development and maintenance of the obese state.

Socioeconomic conditions clearly play an important role in the development of obesity. Excess body weight is 7 to 12 times more frequent in women from lower social classes than in women from the upper social classes (40,103). Among men, social class has a much smaller relationship to being overweight (12,103). In a study by Hazuda, et al., they examined the effects of acculturation and socioeconomic status on Mexican-American men and women, and reported a linear decline in prevalence of obesity and diabetes with increased acculturation and socioeconomic status (47). The relationship of obesity to socioeconomic status could possibly be the strong prejudice in this country against obese persons, evidenced by discrimination in both academic and work settings (114).

Only a few cohort studies have analyzed the effect of socioeconomic status on the development of obesity among adults. The Finnish study by Rissanen, et al.(99), found greater risk of weight gain among those of low socioeconomic status. Three cohort studies (41,106,116) have addressed the relationship between obesity during adolescence or young adulthood with later socioeconomic status. All three studies supported a negative effect of obesity on socioeconomic status in both men and women.

Ford, et al. (29), reported that women of higher socioeconomic status spend significantly more time each week in leisure-time physical activity, job-related physical activity, and household physical activity than do lower socioeconomic women. Men of lower socioeconomic status spent significantly more time each week walking and doing household chores, whereas higher socioeconomic status men tended to be more active in leisure-time physical activity. These data suggest important differences in physical activity among population subgroups.

D. Psychological Factors

In addition to the commonly recognized medical complications associated with morbid obesity such as hypertension and diabetes mellitus, research now suggest possible psychological disorders related to severe obesity (30,60,90,91,112,124).

In 1993, the Swedish Obese Subjects (SOS) intervention study reported levels of anxiety and depression in which the "psychiatric morbidity" level was more often seen in the obese (124). Furthermore, recorded sense of "mental well-being" was less favorable among the obese population when compared to chronically ill or injured patients, such as rheumatoid patients, cancer survivors or spinal chord injured person (124).

In 1995, Kolotkin et al.(60), reported that the impact of weight on quality of life generally worsened as the patients' size increased. However, with women,

feeling overweight at all BMIs had a substantial negative impact on self-esteem and sexual life. Interestingly, the negative effect of weight on self-esteem and sexual life was greater in women than men. As age increased, both men and women reported less impact of weight on self-esteem and social/interpersonal life. However, both sexes reported reduced mobility due to weight with increasing age.

Rand and Macgregor have further documented the problems of the severely obese (90,91). A 20-item questionnaire was addressed to 57 patients before weight loss surgery. All patients reported feeling unattractive. Eighty-one percent felt that people always talked behind their backs at work. A majority indicated frequent discrimination when applying for jobs and disrespectful treatment by the medical profession (90). Fourteen months following the gastric bypass surgery (after a mean weight loss of 50 kilograms), their reports dramatically improved (90). Furthermore, in spite of the strong tendency for people in general to evaluate their own worst handicap as less disabling than other handicaps, formerly obese patients did not. One hundred percent of this gastric bypass population said that they would prefer to be normal weight even if it meant being deaf, dyslexic, diabetic or having bad acne. Ninety percent said that they would prefer to have a leg amputated or to be legally blind rather than to be morbidly obese again (91).

E. Other Environmental Variables

Education level (33) has been implicated as a predictor of body weight and activity level. A study of 26,000 Danish young men, who underwent the mandatory examination at draft boards, showed an inverse J-shaped relationship between educational level and BMI (126). Below the median BMI there was a weak rise in educational level with greater BMI status, whereas the educational level dropped steeply with higher BMI values above the median BMI. Sorensen reported that risk of development of obesity during adult life is inversely related to

educational level at baseline (117).

Preliminary results from other studies have suggested that pregnancy may contribute to the propensity to develop obesity, especially after the third or fourth child (104). Rossner suggested that increases in weight associated with pregnancy may represent a significant contribution to severe obesity (104). In 1993, our group at Cardiovascular Genetics Research conducted a pregnancy study (51) and concluded the following:

1. The number of pregnancies does not affect the amount of weight gained after the last pregnancy;
2. Weight gained during pregnancy is similar among all pregnancies except for the first pregnancy in the morbidly obese;
3. Morbidly obese women gained more weight during pregnancy than controls only for the first pregnancy; and
4. Weight loss after delivery was less in the morbidly obese than the controls, but not significantly.

These findings suggested three main speculative ideas:

1. Women who develop morbid obesity have slightly less weight loss after delivery and greater between-pregnancy weight gain than controls;
2. The number of pregnancies does not affect the amount of weight gained after the last pregnancy; and
3. While multiparity may augment weight gain in morbidly obese women, it is probably not a primary factor in the later development of morbid obesity.

Health status (i.e., diabetes), medication use, weight loss history, cigarette use (63), alcohol consumption (49,62), and head injury (13) have also been suggested as contributing factors in the development of obesity. Religious affiliation has also been found to be predictive of obesity, with the prevalence being higher among Jews, followed by Catholics and lowest among Protestants (77).

III. CONCLUSION

In summary, past research has explored behavorial practices, such as physical activity and dietary intake, of the morbidly obese population in comparison to normal weight individuals. However, very limited data have been collected on the functional status and emotional and mental well-being of the severely obese population in relation to a normal weight population. In an effort to further understand the relationship of these behavorial influences (physical activity, dietary intake and emotional/mental well-being) to morbid obesity, this study compared a cohort of morbidly obese men and women to similar age normal weight siblings. The use of normal weight siblings of severely obese subjects helps match the groups for previously shared household factors. Common childhood environments reduces the likelihood that factors other than those being tested are responsible for differences identified in the analysis.

Furthermore, research studies have explored the environmental and genetic influence on obesity and found that both genes and a shared environment can endow members of a family with a predisposition to obesity. These studies conclude that morbid obesity most likely results from the accumulation of environmental factors over time in genetically susceptible persons. Despite these findings, limited research has examined common behavorial influences such as emotional and physical well-being, physical activity and dietary intake in relation to the degree of family aggregation of obesity. In a previous study, our group compared biochemical and anthropometric variables of severely obese probands selected from families where two or more first degree family members were severely obese with probands who were the only severely obese person in their immediate family (See Appendix 11). We found no significant differences in biochemical and anthropometric variables between probands representing families

aggregating and not aggregating for severe obesity, raising the question regarding the extent environmental influences might have on the degree of obesity present in these two family types. To explore this question, this study also focused on quality of life perception, physical activity and dietary intake of both severely obese and normal weight siblings representing families aggregating and not aggregating for severe obesity.

CHAPTER 3: STUDY DESIGN AND METHODS

We compared families with nonfamilial morbid obesity (families with one morbidly obese proband without any morbidly obese first degree relatives or less severe forms of obesity) to families with familial morbid obesity (families where morbid obesity occurs frequently among first degree relatives). We studied 92 familial and 53 nonfamilial morbid obesity families by comparing environmental variables of 3 siblings in familial morbidly obese families (2 sibs morbidly obese; 1 sib normal weight) with 3 siblings of nonfamilial morbidly obese families (1 sib morbidly obese; 2 sibs normal weight). This study primarily focused on employing methods to distinguish between the influence of genetics and environmental factors on morbid obesity, and then determining which variables were significantly associated with nonfamilial and familial morbid obesity.

I. SUBJECTS

A. Morbidly Obese Siblings

All morbidly obese siblings met the criteria for morbid obesity, which was defined as a body mass index (BMI) of 35 kg/m^2 or greater. A BMI of 35 is, on average, approximately 75 pounds over ideal body weight. Ideal weight was determined from the Metropolitan Life Insurance Tables of 1983 after measuring elbow breadth in clinic or using the medium frame and mid-point weight range when clinic data were not available. Siblings recruited but not meeting study criteria (e.g., obese member's BMI less than 35, normal weight sibling's BMI greater than 27, BMI of nonfamilial first-degree relatives greater than 27, etc.) upon data collection were dropped from the study. Additional families (matching on familial or nonfamilial obesity) were then recruited to obtain our current sample

size.

B. Unaffected, Normal Weight Siblings

All unaffected siblings met the criteria for normal weight, which was defined as a BMI of less than 27 kg/m^2 for both men and women. The upper limit of normal weight BMI is approximately 30 pounds over ideal body weight (128).

II. RECRUITMENT OF SUBJECTS

Subjects were recruited from two sources. The first source was identified from a population-based family history database of over 100,000 families. Data were collected from Health Family Tree questionnaires, which are detailed family histories completed by high school students and their parents as part of the Utah school curriculum (52,141). Fifty-four out of the 55 high schools along the Wasatch Front (within a 50 mile radius of Salt Lake City) have participated in this program. There is little difference in participation rates between schools in rural versus urban areas or between high and low income areas. Health information reported by the families includes the report of "usual weight" categorized as: slender or average; 10-49 pounds overweight; 50-99 pounds overweight; or over 100 pounds overweight (See Appendix 1).

From the 100,000 family population-based database, over 4,000 morbidly obese probands and their siblings were initially identified. Of these 4,000 families with one or more morbidly obese members, 290 were potential familial MO families and 487 were potential nonfamilial MO families.

All nonfamilial MO families (487) and a random sample of familial MO families (97) were sent introductory letters (See Appendix 2) and then contacted by telephone to verify the Health Family Tree record and to ascertain their interest as a participant in the study.

Following verification, 440 of the 487 potential nonfamilial MO families and 26 of the 97 potential and randomly selected familial MO families did not meet the defined criteria for these two types of MO families. Therefore, 47 of the nonfamilial MO families and 71 of the familial MO families were identified from the population-based family history database.

The second source of subjects were participating in a very-low-calorie diet, weight-loss program (Optifast, Sandoz Nutrition) operating at 4 different hospitals in Utah. The directors of the respective weight-loss clinics obtained permission from program participants prior to their being contacted for research participation. Individuals giving consent were then recruited by telephone. From this source, 6 nonfamilial MO families and 22 familial MO families were identified.

III. DATA COLLECTION

This research study was approved by the Institutional Review Board at the University of Utah, and consent forms were collected prior to subject participation (See Appendix 3). Participants were informed that identifying information would be removed, and an arbitrary number assigned to their questionnaires.

Data collection occurred at the Cardiovascular Genetics Research Clinic, University of Utah. Questionnaires were distributed to obtain data for the following environmental variables: anthropometrics (current height, current weight, greatest weight, age at greatest weight), dietary intake, energy expenditure, health status, alcohol intake, cigarette use, medication use, weight history, weight loss history, pregnancy history, socioeconomic status, education level, and occurrence of head injury (See Appendices 4, 5, 6, and 7). The questionnaires were mailed with a Caltrac accelerometer, a device designed to measure the energy expenditure of normal daily activity (See Appendices 8 and 9).

A. Dietary Intake Assessment

A 61-item semiquantitative food frequency questionnaire (Willett) was used to obtain estimated nutrient intake (138,139). It was originally created for use as a self-administered, mailed questionnaire in the Nurses' Health Study (139). The questionnaire has been repeatedly validated (in men and women). For example, one case-control study (138) compared the estimated questionnaire nutrient values with those derived from one-year diet records. The questionnaire estimates of mean nutrient intake were within 10% of the mean diet record measurements for 11 of the 18 nutrients evaluated, and the difference was less than 25% for all but one nutrient (total vitamin A). Further validation studies conclude that the expanded semi-quantitative food frequency questionnaire is reproducible and provides a useful measure of intake for many nutrients over a one-year period. Thus, the results of these validation studies have indicated that the semi-quantitative food frequency questionnaire is remarkably robust.

The use of food frequency questionnaires implies that individuals characteristically eat a specific amount of any particular food, and that this amount can be reported with reasonable accuracy. Hunter et al. (53) observed that women consumed a wide range of different size portions of almost all foods in the course of their normal diets. Thus, it is important to note that a source of reduced accuracy in food frequency questionnaires is the large within-person variance in portion size.

The questionnaire consists of two components: a list of foods; and a set of frequency-of-use response categories. The aim of the food frequency questionnaire is to assess the frequency with which certain food items or food groups are consumed during a specified time period (i.e. daily, weekly, monthly, yearly). The fact that this questionnaire is also semiquantitative means that it attempts to quantify usual portion sizes of the food items of interest. Nutrient

content is computed by multiplying the relative frequency that each food item is consumed by the nutrient content of the average portion size, and then multiplying by portion size. In this obesity study, the questionnaire data were recorded on an optical scanning form, and sent to Harvard University for scanning and nutrient analysis. Upon obtaining the nutrition results (See an example in Appendix 10), the computerized nutrient data were merged into our data base for statistical analysis.

B. Energy Expenditure

We measured the energy expenditure of all study participants through the use of the Caltrac accelerometer. The Caltrac accelerometer is designed to assess the energy expenditure of normal daily activity. The Caltrac accelerometer measures vertical acceleration and deceleration of the body, and has the advantage of being small, portable, light-weight and relatively inexpensive. The Caltrac is fixed to the trunk of the body, usually at the waist, where it measures acceleration of the trunk during physical activity. The microcomputer is programmed with the subject's age, height, weight and gender, which is used to convert acceleration to energy expenditure in kilocalories (kcal).

Pambianco et al. (84), evaluated the inter-instrument and inter-session reliability of the Caltrac accelerometer, and measured the validity of this instrument in estimating energy expenditure by comparing it to oxygen uptake (VO_2) values in overweight (men: 55% overweight; women: 29% overweight) and normal weight (men: 5% overweight; women: -3% overweight) subjects while walking on a treadmill. The Caltrac monitors had no significant differences when worn on the right or left side of the waist (both instruments were worn simultaneously) or within the same instrument during multiple observations.

Caltracs were also found to accurately reflect differences in energy expenditures due to sex, body weight, and speed. However, Caltracs consistently over-estimated energy expenditure by an average of 9 - 13%. The Caltrac's overestimation of caloric expenditure was most pronounced in normal weight subjects at higher speeds and obese subjects at lower speeds. The correlations between Caltrac and VO_2 averaged 0.68 - 0.74. They concluded that Caltracs seem well suited for studies of activity level of groups, but may be less useful in estimating an individual's activity. Similarly, Montoye and associates reported a correlation of 0.74 between energy expenditure as estimated by the accelerometer and VO_2 (75).

Haymes and Byrnes (46) examined the accuracy of Caltrac during walking and running and concluded that the Caltrac is a valid indicator of physical activity during walking (correlation coefficient = 0.91), but Caltrac does not adequately discriminate between running speeds of 5-8 mph. Washburn et al. (136), also assessed the Caltrac monitor's ability to measure physical activity in an occupationally active group. They further established the validity and reliability in measuring physical activity over 24 hours.

Major limitations of these sensors include their inability to accurately identify: (1) increases in energy expenditure due to movement up inclines (hills or stairs) or an increase in energy expenditure due to an increase in resistance to movement (increasing the amount of weight lifted or resistance on a cycle ergometer); (2) movement that involves various parts of the body; and (3) the detection of static exercise. However, for our research purposes which include measuring large numbers of people, the Caltrac monitor is the best option.

For our obesity research we asked participants to wear the Caltrac accelerometer for 3 consecutive days and to record their total daily energy expenditure (measured in kcal) and their activity expenditure (measured in kcal) at

the end of each day (just prior to going to bed), and first thing in the morning. Therefore, we obtained a three-day, accumulative calorie record for total energy expenditure and activity expenditure. With the measures taken in the evening and morning we were able to calculate daily values for three consecutive days.

Prior to wearing the Caltrac accelerometer it must be programmed with the participant's gender, age, weight and height. Probands and familial, normal weight siblings screened through our clinic were given their actual height and weight.

-Height measured with a Harpenden anthropometer (Holtain Ltd), with the subject stretched to maximum height.

-Weight measured with a Scaletronix scale (Sharp Co.: Model 695, weighing to 800 pounds).

However, because our nonfamilial, normal weight participants were not screened in clinic, an important element of this proposal is the accuracy of the self-reported weight and height. Several important studies have been conducted to compare the actual measurement of height and weight with self-reported values (79,120). Some reports suggest that the accuracy of the self-reported weight (r=0.99) and height (0.95) is high (66,83,120).

To determine the accuracy of the self-reported weights in the Utah population, our clinical data were compared to 2,500 subjects who first self-reported their height and weight by questionnaire, and were then actually measured for weight and height within two weeks. When differences in self-reported and measured body weight were compared within gender and age groups, the mean difference was within 5 pounds (plus or minus), although at the higher weights the differences were greater than at lower weights.

To determine how self-reported error may have affected the results of this study, weight (in pounds) was altered by subtracting 5 pounds from severely

obese subjects and adding 5 pounds to the normal weight subjects. In so doing, 6 (3%) of 218 affected subjects no longer met the "severely obese" classification criteria (BMI > or = 35), and 16 (10%) of the 153 unaffected subjects no longer met "normal weight" criteria (BMI < or = 27). Based upon this test and our clinic comparisons of self-reported weights versus measured weights and the studies just referenced, and given the fact that all participants were instructed regarding the need for their report to be accurate as possible, we believe the self-reported values were of adequate accuracy for the purpose of classification: affected (severely obese) and unaffected (normal weight).

C. Psychological and Emotional Well-Being

The 36-item short-form (SF-36) was constructed to survey health status in the Medical Outcomes Study (MOS), a four-year observational study designed to examine the influence of specific characteristics of providers, patients and health systems on outcomes of care (125). The major goal of MOS was to advance state-of-the-art methods used for routine monitoring of patient outcomes in medical practice and clinical research (125).

The SF-36 was designed for use in clinical practice and research, health policy evaluations and general population surveys. The survey was constructed for self-administration by persons 14 years of age and older. The SF-36 addresses general health concepts not specific to any age, disease or treatment group. It measures perceptions regarding basic human experiences such as functional status, emotional well-being and overall health. The SF-36 was standardized in 1992, and has been used in many studies. It has been proven to be as reliable, consistent, reproducible and valid as longer health status instruments. The popularity of SF-36 appears to be largely driven by its brevity yet comprehensiveness (134). It provides a yardstick for health status comparisons in subjects with the same

condition and between those with different conditions.

The SF-36 assesses eight health concepts: (1) limitations in physical activities because of health problems; (2) limitations in social activities because of physical and emotional problems; (3) limitations in usual role activities because of physical health problems; (4) bodily pain; (5) general mental health (psychological distress and well-being); (6) limitations in usual role activities because of emotional problems; (7) vitality (energy and fatigue); and (8) general health perceptions (134).

In summary, the SF-36 is a generic, self-completion health status questionnaire which contains 36 items, analyzed as 8 scales and a 1-item measure of change in health. The possible range of the SF-36 scale scores are 0 to 100, with zero indicating the lowest possible score (poor health), and 100 the highest possible score (good health). A score is calculated for each of the areas by summing responses to individual items and converting, by a scoring algorithm, to a scale from 0 to 100. (This follows scoring algorithms as suggested by its developers (135) and permits comparisons with published Medical Outcomes Study results and national norms.)

D. <u>Additional Questionnaires</u>

Three additional health history questionnaires were given to participants: Individual Form, Medication Form and Weight History and Activity Questionnaire (See Appendix). The questionnaires were designed to assess the self-reported general health history of the individual (medication use, alcohol use, cigarette use, health/disease status and occurrence of head injuries) as well as socioeconomic, education and religious status, specific information regarding health factors influential to weight gain and the individual's weight and weight-loss history. The weight history questionnaire also included a section pertaining to physical activity.

Select physical activity questions were taken from the validated and standardized questionnaire derived by Paffenbarger and colleagues (82). The questionnaire was derived largely from their epidemiological experience with the Harvard Alumni Health Study (81). Each question from the questionnaires were coded and entered into the computer for analysis.

IV. DATA ANALYSIS

Data from all questionnaire tables and from the Willett food frequency reports software were merged into a SAS data set. Study and participant qualifications were defined for inclusion into the data set. Variable and missing value coding, definitions, and equations were programmed. Prior to statistical analysis, one of the two affected (morbidly obese) familial sibs was randomly selected and paired to the remaining unaffected familial sib, and one of the two unaffected (normal weight) nonfamilial sibs was randomly selected and paired with the remaining affected nonfamilial sib. This pairing method facilitated comparison of familial versus nonfamilial sibships.

Following randomization and pairing of sibships, variables were adjusted for age and sex in a general linear model. These residual variable values were then statistically analyzed by repeated measures analysis of variance to test for differences between MO and normal weight participants. The siblings from the same family represent the repeated measure. When adjusting for whether the MO and normal weight participants came from familial or nonfamilial MO families, 3 of the 49 variables had a significant effect for familiality. However, the effect of familiality did not change the significance of the test for these 3 variables: saccharin intake, weekend hours spent in vigorous activity and percent vegetable fat in the diet (these variables were significantly different between the MO and normal weight subjects before and after the adjustment for familiality.)

A Student's t-test was used to assess differences in familial versus nonfamilial obesity and familial versus nonfamilial unaffected status, and to determine whether mean intrapair differences between affected and unaffected siblings differed in nonfamilial and familial pedigrees. For categorical variables or variables not normally distributed, comparisons were calculated with a Chi-squared, McNemars or Wilcoxon rank sum test. The SAS statistical package was used for the calculations (107).

V. SAMPLE SIZE JUSTIFICATION

All the tests detailed in the SPECIFIC AIMS section are equivalent to a two-sample t-test in which we can detect a significant difference of 0.50 standard deviation at a p-value of 0.05 with 82% power.

VI. PREDICTED OUTCOME

We proposed to show the degree to which environment is related to morbid obesity, and to define the most significant environmental variables with which to focus on in a subsequent intervention study.

The investigators involved with this study are currently in the process of gathering data to further investigate the genetics of obesity. If the data from this study support a genetic hypothesis for morbid obesity, the results would suggest that environment plays different roles in nonfamilial and familial morbid obesity families. Specifically, nonfamilial affected siblings would have an environmental cause for their morbid obesity and familial-affected siblings would not differ environmentally from their unaffected siblings, except for any differences resulting from the greater weight gain.

If we find that environment plays a similar role in nonfamilial and familial obesity, we can conclude either that the cause of the morbid obesity is genetic and

only one nonfamilial sibling carries the gene or there is no major gene and the contributor to the morbid obesity in both familial and nonfamilial morbid obesity families is environmental.

This research endeavor should naturally lead to other questions and hypotheses regarding the cause and treatment of obesity.

CHAPTER 4

Functional Status and Well-Being, Nutrient Intake and Physical Activity Among Severely Obese Subjects[1]

[1]This chapter will be submitted for publication in Obesity Research

Functional Status and Well-Being, Nutrient Intake and Physical Activity Among Severely Obese Subjects

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RUNNING TITLE: Functional Status in Morbid Obesity

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ABSTRACT

The unique component of this study was the analysis of behavioral influences (health-related quality of life issues, nutrient intake and physical activity) in 145 siblings raised together in the same family, with one sibling classified as severely obese (BMI > or = 35 kg/m^2) and the other as normal weight (BMI< or = 27 kg/m^2). All participants completed the standardized and validated SF-36 health status questionnaire, a semi-quantitative food frequency questionnaire, and a physical activity questionnaire, as well as study-specific questionnaires on weight loss history and socioeconomic status. Caltrac accelerometers were worn for 3 consecutive days by all subjects to assess daily activity expenditure. Results of this study found: (1) All SF-36 functional status and well-being scores were significantly lower in MO participants when compared to normal weight participants; (2) Percent fat and percent protein intake and total caloric intake were significantly higher among the MO group, while weight-adjusted total caloric intake, percent carbohydrate intake and carbohydrate/fat ratio were significantly lower in the MO subjects; and (3) Weight-adjusted physical activity measured by the Caltrac activity monitor was significantly lower in the MO siblings. These findings suggest that morbid obesity is associated with lower reported levels of perceived physical and emotional well-being, and that environmental influences such as nutrient intake and physical activity are highly related to severe obesity. The uniqueness of the sibling study design allowed us to theorize probable causes of the severe obesity as the siblings shared both genes and a previous home environment. We concluded that the most probable reason for the obesity is due to the interaction of behaviors with a nonshared genetic inheritance.

INDEX TERMS: SF-36, Quality of Life, Nutrient Intake, Caloric Intake, Fat Intake, Physical Activity, Caltrac Accelerometer, Body Mass Index, Obesity

INTRODUCTION

Morbid obesity is well recognized as a major risk for early disability and death (4,5,13,21,37,45,53,74,75). Past research has explored behavioral practices, such as physical activity and dietary intake (1,3,7,8,10,14,15,16,30,34,57,60), of the severely obese population in comparison to normal weight individuals. However, very limited data have been collected on the functional status and emotional and mental well-being of the severely obese population in relation to a normal weight population. In 1993, the Swedish Obese Subjects (SOS) intervention study reported that the level of anxiety and depression was more frequent and severe in the severely obese participants (71). Furthermore, recorded sense of "mental well-being" was less favorable among the severely obese population when compared to chronically ill or injured patients, such as rheumatoid patients, cancer survivors or spinal chord injured persons (71). Diet and physical activity research has suggested that the extent of obesity in susceptible individuals is increased by long-term exposure to a given diet consisting of excess caloric intake or of an altered macronutrient composition such as sweet or high-fat foods (14,15,19,35,40,43,60,64,65,69,73). Data on energy expenditure indicates that physical activity is inversely related to indicators of body fatness and is a predictor of future weight gain (10,34,57,59,81).

In an effort to further understand the relationship of these behavioral influences (physical activity, dietary intake and emotional/mental well-being) to morbid obesity, this study compared a cohort of severely obese men and women to similar age normal weight siblings. The use of normal weight siblings of severely obese subjects helps match the groups for previously shared household factors. This matching on common environments reduces the likelihood that factors other than those being tested are responsible for differences identified in the analysis. In addition to monitoring physical activity and nutritional practices, this study

utilized the validated SF-36 (36-item short form) to assess general health status and psychological and emotional well-being.

METHODS

Subjects

All severely obese individuals in this study met the criteria for morbid obesity, defined as a body mass index (BMI) of 35 kg/m^2 or greater. We found a BMI of 35 kg/m^2 was on average approximately 75 pounds over ideal body weight when ideal weight was determined from the Metropolitan Life Insurance Tables of 1983 using elbow breadth, or using the medium frame and midpoint weight range when clinic data were not available. All unaffected participants met the criteria for normal weight, which we defined as a BMI of 27 kg/m^2 or less for both men and women. This normal weight cut point is approximately 30 pounds over ideal body weight (74).

Subjects were recruited from two sources. The first source was identified from a population-based family history database of over 100,000 families. Data were collected from Health Family Tree questionnaires which are detailed family histories completed by high school students and their parents as part of the Utah school curriculum (25,84). There is little difference in participation rates between schools in rural versus urban areas or between high and low income areas. Health information reported by the families included the report of "usual weight" categorized as: slender or average; 10-49 pounds overweight; 50-99 pounds overweight; or over 100 pounds overweight. One hundred eighteen (118) of the 145 sibpairs were identified from the family history database.

A random sample of families with both severely obese and normal weight siblings were sent introductory letters and then contacted by telephone to verify

the Health Family Tree record and to ascertain their interest as participants in the study.

The second source of subjects (27 sibpairs) were participating in a very-low-calorie diet, weight-loss program (Optifast, Sandoz Nutrition) operating at 4 different hospitals in Utah. The directors of the respective weight-loss clinics obtained permission from program participants prior to their being contacted for research participation. Individuals giving consent were then recruited by telephone.

Data Collection

This research study was approved by the Institutional Review Board at the University of Utah, and individuals gave written consent prior to participation. Data collection took place over a 36-month period from January 1994 through December 1996 at the Cardiovascular Genetics Research Clinic, University of Utah. Questionnaires were distributed to obtain data for the following environmental variables: anthropometrics (current height, current weight, greatest weight, age at greatest weight), SF-36 health status values, dietary intake, physical activity levels, alcohol intake, cigarette use, socioeconomic status, and education level.

In addition to all subjects receiving and completing above mentioned questionnaires, severely obese and normal weight subjects were given a Caltrac activity monitor (Muscle Dynamics Fitness Network, Torrance, CA). The Caltrac was fixed to the trunk of the body to measure acceleration of the trunk during physical activity. Each Caltrac microcomputer was programmed with the subject's age, height, weight and gender. The participants were asked to wear the Caltrac accelerometer for 3 consecutive days and to record their total daily energy expenditure (measured in kcal) and their activity expenditure (measured in kcal) at

the end of each day (just prior to going to bed), and first thing in the morning. With the measures taken in the evening and morning we were able to calculate daily values for three consecutive days. The monitor was mailed back after wearing the monitor for three days. One hundred percent of the subjects included in the activity expenditure analysis wore the monitor for 1 full day. Ninety six percent wore the Caltrac for 2 days and 92% wore the monitor for the complete 3 day period.

Data for the three areas of behavioral influences (physical activity, dietary intake and emotional/mental well-being) were collected in 145 sibpairs. Each sibpair comprised one severely obese sibling and one normal weight sibling. Nutrition data were completed by 132 sibpairs and the activity questionnaire was completed by 144 sibpairs. The Caltrac activity monitor data were complete for 134 sibpairs. Height and weight data were measured at the Cardiovascular Genetics Research Clinic on 76 severely obese and 55 normal weight participants. Self-reported height and weight data were received on 68 severely obese and 89 normal weight participants.

Total caloric intake and energy expenditure values were divided by weight in kilograms to adjust for differences in weight. A weight adjustment provides more comparable values as energy intake and expenditure are highly related to body size. However, a lean body mass adjustment (value not obtained) would have been preferable for body-size associated variables.

Instruments

Physical Activity Questionnaire

Select physical activity questions were taken from the validated and standardized physical activity questionnaire designed by Paffenbarger and colleagues (48,49). The physical activity questions were qualitative concerning

such items as: attitudes on physical activity, number of exercise sessions per week, blocks walked or flights climbed per day, usual pace of walking and level of exertion in exercise. The final section of the questionnaire required the participants to estimate and breakdown the hours of an average weekday and weekend by activity type (sleeping, sitting, light activity, moderate activity, and vigorous activity).

SF-36 Questionnaire

The 36-item short-form (SF-36) was designed to survey health status in the Medical Outcomes Study (MOS), a four-year observational study designed to examine the influence of specific characteristics of providers, patients and health systems on outcomes of care (72). The SF-36 addresses general health concepts not specific to any age, disease or treatment group. It measures basic human values such as functional status, emotional well-being and overall health. The SF-36 was standardized in 1992, and has been used in many studies. It has been proven to be as reliable, consistent, reproducible and as valid as longer health status instruments. The popularity of SF-36 appears to be largely driven by its brevity yet comprehensiveness (79). It provides a yardstick for health status comparisons in subjects with the same clinical condition and between subjects with different clinical conditions.

The SF-36 assesses eight health concepts: (1) limitations in physical activities because of health problems; (2) limitations in social activities because of physical or emotional problems; (3) limitations in usual role activities because of physical health problems; (4) bodily pain; (5) general mental health (psychological distress and well-being); (6) limitations in usual role activities because of emotional problems; (7) vitality (energy and fatigue); and (8) general health perceptions (79). Definitions of each scale are listed in Table 1. Thus, the SF-36 is a generic, self-

completion health status questionnaire which contains 36 items, analyzed as 8 scales and a one-item measure of change in health. The possible range of the SF-36 scale scores are 0 to 100, with zero indicating the lowest possible score (poor health), and 100 the highest possible score (good health). A score is calculated for each of the areas by summing responses to individual items and using a scoring algorithm converting to a scale from 0 to 100. Using the scoring algorithms as suggested by its developers (80) permits comparisons with published Medical Outcomes Study results and national norms.

(See Table 1)

Willett Food Frequency Questionnaire

A 61-item semiquantitative food frequency questionnaire was used to obtain estimated nutrient intake (26,58,61,82,83). Validation studies have indicated that the semi-quantitative food frequency questionnaire is remarkably robust (26,58,61,82,83). The questionnaire consists of two components; a list of foods and a set of frequency-of-use response categories. The aim of the food frequency questionnaire is to assess the frequency with which certain food items or food groups are consumed during a specified time period (i.e. daily, weekly, monthly, yearly). The fact that this questionnaire is also semiquantitative means that it attempts to quantify usual portion sizes of the food items of interest. Nutrient content is computed by multiplying the relative frequency that each food item is consumed by the nutrient content of the average portion size, and then multiplying by the number of portions.

Statistical Analysis

Means and standard deviations were calculated to describe the basic

characteristics of the patient population. Prior to statistical analysis, variables were adjusted for age and sex in a general linear model (GLM, 62). The residuals from this model were then statistically analyzed by repeated measures analysis of variance to test for differences in study variables between severely obese and normal weight participants. The siblings from the same family represent the repeated measure. For categorical variables or variables not normally distributed, comparisons were calculated with a Chi-squared or Wilcoxon rank sum test.

RESULTS

Social/Demographic Characteristics

Detailed in Table 2 are the age, BMI, gender distribution, and social/demographic characteristics of the patient population by affected status (severely obese(affected) and normal weight (unaffected)). There were no significant differences in age between the normal weight and severely obese participants. The severely obese subjects had a mean BMI of 44.7 kg/m^2 compared to 24.4 kg/m^2 in the normal weight subjects ($p<0.0001$). Gender distribution, marital status, education level and income level did not differ significantly between the severely obese and normal weight siblings. However, if the annual household income level had been compared as a one-sided test, a significant difference would have been reported with a trend towards more normal weight siblings making $50,000 per year than their affected counterparts ($p=0.035$).

(See Table 2)

Functional Status and Emotional Well-Being

The eight scale-score comparisons between affected and unaffected participants

are reported in Table 3. Severely obese individuals perceive their general health to be 20.4% poorer and more likely to get worse than normal weight individuals ($p<0.0001$). Furthermore, the severely obese group report their pain as 11.4% more severe and limiting ($p<0.0001$). Severely obese participants are 23.3% more limited in performing all physical activities including bathing and dressing ($p<0.0001$), and they also have 26.6% more problems with work or other daily activities as a result of physical health ($p<0.0001$).

Concerning vitality status, severely obese participants reported energy levels (frequently feeling tired and worn-out) 18.7% lower than normal weight participants ($p<0.0001$). Severely obese participants that emotional problems disrupt their work or daily activities 16.3% more often than unaffected individuals ($p=0.0012$). Feelings of nervousness and depression were 7% more prevalent in severely obese subjects ($p=0.0008$). Finally, severely obese subjects reported having more (11.3%) interferences with normal social activities due to physical and emotional problems than did their normal weight counterparts ($p<0.0001$).

(See Table 3)

Nutrient Intake

Nutrient intake estimates are summarized by affected and unaffected status in Table 4. Severely obese subjects consumed over 350 more total calories than normal weight participants prior to adjusting for body weight ($p<0.0001$). However, after adjusting for body weight, severely obese participants at almost 10 kcal/kg fewer kilocalories per kilogram of body weight than their normal weight counterparts ($p<0.0001$).

Fat, protein and carbohydrate intakes were all significantly greater in the severely obese individuals (See Table 4). The percent fat intake of the severely

obese participants was 3% higher than the normal weight participants ($p<0.0001$). Percent animal fat, vegetable fat, saturated fat and monounsaturated fat were all significantly greater in the obese siblings (See Table 4). The carbohydrate/fat ratio was significantly lower in severely obese individuals (3.7 vs. 4.6; $p<0.0001$). Percent carbohydrate intake was 3% lower in the severely obese individuals ($p=0.0003$). Percent protein intake was 1% higher in the severely obese siblings ($p=0.02$). Dietary fiber and caffeine intake did not differ between severely obese and normal weight siblings. Saccharin intake was 8 milligrams higher in the severely obese participants ($p=0.05$).

(See Table 4)

Physical Activity

Table 5 summarizes the physical activity values measured by both the Caltrac accelerometer and the activity questionnaire. Severely obese participants averaged over 350 kcal greater total energy expenditure (measured by the Caltrac accelerometer over a 24 hour period) than the normal weight siblings ($p<0.0001$). However, after weight-adjusting total daily energy expenditure, the severely obese subjects used 7.5 fewer calories per kilogram body weight than the normal weight subjects ($p<0.0001$). Total daily activity expenditure did not differ between affected and unaffected siblings. However, with the weight-adjustment, activity calories were 3.5 lower per kilogram body weight in the severely obese versus normal weight participants ($p<0.0001$).

From the activity questionnaire, the obese population reported fewer blocks walked per day and a slower walking pace than the normal weight participants. The obese subjects reported exercising fewer times per week than their normal weight counterparts, exercising at a lower intensity and indicating that they ought

to do more physical activity. Flights of stairs climbed per day was also significantly less in the obese participants. Part of the activity questionnaire required the participants to estimate hours of activity type (sleeping, sitting, light activity, moderate activity and vigorous activity) spent per average weekday and weekend. The obese reported fewer hours spent in vigorous activity on weekdays, fewer hours of moderate activity on weekdays and weekends, more hours spent sitting on weekdays, and more hours spent sleeping on the weekends.

(See Table 5)

Cigarette Use and Alcohol Consumption

Cigarette use was measured in number of smoking years, and alcohol use was reported in grams of alcohol consumed (See Table 4). Alcohol consumption and cigarette use did not differ between severely obese and normal weight participants (cigarette years: p=0.84; alcohol: p=0.23).

DISCUSSION

The unique component of this study was the analysis of behavioral patterns in siblings raised together in the same family, with one sibling severely obese (BMI>= 35) and the other sibling normal weight (BMI <= 27). Because of the potential difficulty in locating twins with such extremes in body size, we chose to examine these behavioral influences in sibpairs. Using this design, this research provides genetic and environmental insight to morbid obesity given the fact that these sibpairs shared approximately 50 percent of their genes and a common environment, yet one developed an extreme form of obesity and the other maintained normal weight status.

An important element of this study includes the accuracy of the self-reported weight, height, and greatest weight for those participants who were unable to participate in a clinic visit for either location or funding reasons. Several studies have compared the actual measurement of the height and weight with self-reported values (46,50,70). These reports suggest that the accuracy of the self-reported weight and height is highly correlated to measured height (0.95) and weight (r=0.99). To determine the accuracy of the self-reported weights in the Utah population, our clinical data were compared to 2,5000 subjects who first self-reported their height and weight by questionnaire, and were then actually measured for weight and height within two weeks. When differences in self-reported and measured body weight were compared within gender and age groups, the mean difference was within 5 pounds (plus or minus), although at the higher weights the differences were greater than at lower weights. To determine how self-reported error may have affected the results of this study, weight (in pounds) was altered by subtracting 5 pounds from severely obese subjects and adding 5 pounds to the normal weight subjects. In so doing, 6 (3%) of 218 affected subjects no longer met the "severely obese" classification criteria (BMI > or = 35), and 16 (10%) of the 153 unaffected subjects no longer met "normal weight" criteria (BMI < or = 27). Based upon this test and our clinic comparisons of self-reported weights versus measured weights and the studies just referenced, and given the fact that all participants were instructed regarding the need for their report to be as accurate as possible, we believe the self-reported values were of adequate accuracy for the purpose of classification: affected (severely obese) and unaffected (normal weight).

Three main areas of behavioral practices were explored: health-related quality of life (HQL) or emotional and physiological well-being, dietary intake and physical activity levels. Health-related quality of life was described in relation to

morbid obesity using the SF-36 questionnaire. Health-related quality of life represents the overall effect of illness and subsequent therapy on a patient, as reported and evaluated by the patient (66). The broad domains that contribute to overall HQL include physical and mental functioning and well-being, social and role disability, and general health perceptions (78). Standardized assessments of HQL make it possible to quantify the burden of specific illness (47).

We found that, as initially hypothesized, all SF-36 functional status and emotional well-being scores were significantly lower in severely obese participants when compared to normal weight participants. This hypothesis was based on reports of: increased psychological distress in obese persons (77); improvements in morale following weight loss (85); and associated physical handicap of severe obesity with serious work- and recreation-related disabilities (2). Moreover, severely obese persons are daily confronted by physical environments that limit their mobility, constrain their recreational activities and subject them to humiliation (77).

Our results pertaining to functional status and emotional well-being differences in severely obese versus normal weight participants agree with other studies. Kolotkin and colleagues (33) reported that quality of life generally declined as the patients' weight increased. They reported that quality of life worsened in the areas of health, social and interpersonal relationships, work, mobility, self-esteem, sexual life and activities of daily living.

In 1993, Sullivan et al., published a portion of their Swedish Obese Subjects (SOS) intervention study in which they measured baseline health and psychosocial functioning in 1,743 subjects (71). Their severely obese participants reported distinctly poorer current health and less positive mood states than the reference subjects, women being worse than men. Anxiety and/or depression on a level indicating psychiatric morbidity were more often seen in the obese and women

reported more affliction than men. Furthermore, the average mental well-being was worse than in chronically ill or injured patients, such as rheumatoid, cancer survivors and spinal cord injured persons (71).

Rand and Macgregor have further documented the problems of the severely obese (54,55). A 20-item questionnaire was addressed to 57 patients before weight loss surgery. All patients felt unattractive, 81% felt that people always talked behind their backs at work, and a great majority indicated that they have been always or usually discriminated against when applying for jobs and treated disrespectfully by the medical profession (54). Dramatic improvement in these areas was experienced 14 months after the gastric bypass surgery, after a mean weight loss of 50 kilograms (54). Furthermore, in spite of the strong tendency for people in general to evaluate their own worst handicap as less disabling than other handicaps, formerly obese patients viewed their obesity handicap as very disabling. One hundred percent said that they would prefer to be normal weight even if it meant being deaf, dyslexic, diabetic or having bad acne. Ninety percent said that they would prefer to have a leg amputated or to be legally blind rather than to be severely obese again (55).

The second behavioral influence examined was nutrient intake in relation to obesity using a 61-item semiquantitative food frequency questionnaire (26,58,61,82,83). It has been established that dietary data based on self-reported intake must be interpreted with care, as under reporting often occurs, particularly in obese subjects. Lansky and Brownell found that obese patients under reported daily caloric intakes by one-third or more (35). Lichtman, et al. (38), studied 9 women and 1 man (BMI=33.8) who repeatedly failed to lose weight even thought they reported restricting their caloric intake to less than 1200 kilocalories per day. Lichtman evaluated total energy expenditure and actual energy intake in these 10 subjects for 14 days by indirect calorimetry. Total energy expenditure and resting

metabolic rate in these participants were within 5 percent of the predicted values for body composition, however they were found to underreport their actual food intake by an average of 47 percent. Furthermore, Johnson, et al. (31), found that under reporting of energy intake increased with the amount of adiposity in women. Acquiring accurate dietary intake data from obese patients is notoriously difficult (23).

With the semiquantitative food frequency questionnaire used in the present study, we found that severely obese individuals consumed significantly more total calories than the normal weight participants. We had hypothesized that severely obese participants' total and adjusted total caloric intake would be significantly greater than the normal weight siblings. The total caloric intake was significantly higher in the severely obese (MO: 2191.5 kcal; normal weight: 1824.2 kcal), however the weight-adjusted caloric intake of the severely obese was significantly less than the normal weight participants (MO: 16.9 kcal/kg; normal weight: 26.2 kcal/kg). To compare self-reported versus measured caloric intake, the previously mentioned study by Lichtman (38) et al. found that the subjects reported their energy intake during the 14-day study period at 1,028 kcal per day, whereas their actual energy intake was 2,081 kcal per day ($p<0.05$). The measured caloric intake value of 2,081 kcal is comparatively similar to the reported 2,191 kcal per day found in our study's obese participants.

Similar to our findings, a recent article in association with the Swedish Obesity Study (SOS) reported that unadjusted mean energy intake measured via questionnaire was significantly higher in obese women (obese women [BMI=40.5]: 2,730 kcal; nonobese women [BMI=23.7]: 2,025 kcal; $p<0.0001$) (39). Lawson et al.(36) measured dietary intake with nutritional diaries in which participants recorded all foods consumed during a two-week period. They found that obese participants (BMI=37.4) consumed an average of 2,030.4 kcal per 24

hour period with a weight-adjusted total caloric intake of 24.1 kcal/kg. The nonobese (BMI=19.1) participants' total caloric intake averaged 1,828.9 kcal/24 hour period with a weight-adjusted intake of 32.2 kcal/kg. The weight-adjusted caloric intake between the obese and normal weight participants were significantly different ($p<0.01$); the total caloric intakes between the two groups did not differ significantly.

In lieu of these reports, most available studies describing the relationships between severe obesity and caloric intake report that obese subjects do not eat more than their counterparts (3, 22,34,57). Interestingly, analysis of the NHANES I data, which was based on 24-hr food recalls, found a negative correlation between overeating and overweight (7). The most obese women appeared to be consuming the fewest calories. Furthermore, Kromhout reported greater obesity was associated with lower caloric intake in obese men (34).

Although human nutrition data is still limited in the severely obese population, recent dietary intake studies suggest that the habitual diet of obese men and women may be rich in fat (40,60, 73). Our study supports these findings as the severely obese population was significantly higher in total fat intake and all forms of measured fat intake: animal fat, vegetable fat, saturated fat and monounsaturated fat. These results confirmed our initial hypothesis which predicted that the severely obese participants' fat intake would be significantly greater than the normal weight siblings. The wide availability of high fat foods in the typical American diet may be an important risk factor, promoting the expression of obesity among susceptible individuals. Romieu et al., reported that obese women consumed more fat calories than did lean women and had a lower dietary carbohydrate:fat ratio. For this study, the carbohydrate:fat ratio was also significantly lower in the severely obese group. The SOS study also found the proportion of total energy intake from fat was significantly higher in obese women

than nonobese women (39). Dreon et al., reported that high levels of body fat were correlated with the amount of fat in the diet (14). Therefore, excessive total caloric intake, as well as fat intake, appears to be predictive of morbid obesity.

Cleave, Burkitt and Trowell used epidemiological observations to link low dietary fiber intakes to the occurrence of obesity and other diseases common in Western society (9,11). Cleave suggested that most of the obesity prevalent in industrialized society is due to replacement of crude carbohydrate by refined, low fiber foods. Lovejoy and DiGirolamo reported that obese subjects consumed significantly less fiber and carbohydrate than did lean subjects (41).
Alfieri, et al., also reported a lower fiber intake in their obese participants than in the lean participants (1). In contrast, we found no significant difference in dietary fiber intake between our severely obese and normal weight subjects. The severely obese subjects were found to consume a lower percentage of their diet from carbohydrates than their counterparts. This study would support the notion that fiber is not related to the sustenance of obesity.

These significantly different dietary findings between affected and unaffected siblings are particularly interesting in that a recent study by Perusse et al. (52), reported that after examining 375 families no significant genetic effect was found for intake of any nutrient tested, and cultural inheritance was found to be more important than genetic inheritance. Their results suggest the average genetic influence on nutrient intake is negligible and that nongenetic effects associated mainly with home environment are the major affecters of energy intake. One of the unique aspects of our study is that we controlled for a similar home environment in youth. The shared household environment reduces the likelihood that other unmeasured factors are responsible for the differences in weight gain. Interestingly, Sellers et al.(68), reported that dietary variables correlate between adult siblings even after they no longer live together in the same household.

Sellers' data showed that dietary patterns among adult siblings living apart are more alike than could be predicted by their sharing a common home environment (alike as has been described for monozygotic twins)(17,23,24,32,63). In light of the fact that our sibpairs differ significantly in caloric intake, fat intake and carbohydrate intake, the question remains, "Which came first, the diet or the obesity?" One could argue that the obesity promoted increased consumption due to energy requirement or, on the other hand, the obese or normal weight siblings chose to not share in common familial eating patterns.

It was interesting to find saccharin intake to be significantly higher in the severely obese as we had assumed soft drink consumption to be greater in the severely obese subjects. Both cigarette use and alcohol consumption did not differ between the two groups. These subjects were recruited from a population with a low smoking and alcohol consumption prevalence.

The third environmental practice compared was physical activity levels in severely obese and normal weight sibpairs. Physical activity was determined by a Caltrac accelerometer. Activity variables were recorded in kilocalories and adjusted for weight in kilograms. The severely obese subjects used more calories per day than their counterparts; however, after adjusting for differences in weight, the severely obese used significantly less calories per kilogram body weight. The severely obese participants had significantly lower weight-adjusted activity expenditures than the normal weight subjects. Their perspectives on physical activity measured by the activity questionnaire supported the measured Caltrac values. These findings correspond directly with our initial hypotheses of lower physical activity levels in the severely obese. Several studies support lower activity levels in severely obese individuals. Kromhout, et al., reported in the Zutphen study that physical activity per kilogram body weight was inversely related to indicators of body fatness (34). Similarly, Ravussin, et al. (57), showed

that low rates of energy expenditure were significant predictors of gain in body weight. Rising et al. (59), reported that obese Pima Indians were less active than their lean counterparts. Their results suggested that obesity is associated with lower levels of physical activity (59). Furthermore, Chirico and Stunkard found that when physical activity was measured by pedometers and activity questionnaires, obese men and women were less active than their lean counterparts (10).

Weinsier et al. (81), conducted a prospective study in which 24 previously obese (post-obese) women were compared with 24 never-obese women of comparable age and body composition. At the beginning of the study, the following measured parameters in the post-obese women were similar to the never-obese controls: mean resting energy expenditure, thermic effect of food, and fasting and postprandial substrate oxidation and insulin-glucose patterns. Four years later, without intervention, the women predisposed to obesity regained essentially all of their lost weight, whereas all of the never-obese women maintained a normal weight. Despite this difference, neither resting energy expenditure, the thermic effect of food, nor the patterns of fasting or postprandial fuel utilization were predictive of long-term weight gain in either group. Only the self-reported physical inactivity was associated with greater weight regain. These results suggest that energy expenditure for physical activity may have a long-term effect on the level of body fat carried by an individual.

Again, the significant difference in sibpairs is intriguing as the few available studies examining the familiality of physical activity report a significant parental transmission in the characteristics of physical activity such as physique, fitness, measured activity levels, temperament (nervous vs calm), and fidgeting (44, 51). An "active temperament" appears to be influenced by heredity. Since spontaneous physical activity or "fidgeting" may account for a substantial fraction of the 24-

hour energy expenditure measured in a respiratory chamber, these data suggest that inherited differences in activity level as a behavior could have a significant impact on daily energy expenditure (56). It is the conclusion of these studies that genetic and/or cultural factors transmitted across generations may predispose a child to be active or inactive. Thus, even with these shared environment and common gene effects influencing activity levels, the affected and unaffected siblings in our study have significantly different behavioral practices.

What are the possible or probable reasons why one sibling is severely obese and the other is not? There are three probable explanations to describe this difference. One possibility is that different behavioral factors are the cause, despite shared childhood environmental influences and common genes. A second is that the nonshared genetic inheritance (e.g., a single gene with large effects) caused the obesity and the behavioral patterns resulted subsequent to the obese status. The third explanation is that the obesity is due to nonshared genetic inheritance with a behavioral interactive background. As the interaction continues, the siblings become more and more distinct. Bouchard has stated: "the genotype determines what can happen and the environment determines what does happen"(6).

In conclusion, health-related quality of life was perceived by severely obese participants to be significantly lower than normal weight siblings in such areas as physical functioning, bodily pain, social activities, psychological distress and well-being, emotional problems, vitality and general health perceptions. Fat intake and total caloric intake were significantly higher, but adjusted total caloric intake was significantly lower in severely obese versus normal weight participants. In both monitor and questionnaire measured activity levels, severely obese individuals had significantly lower activity expenditures than their normal weight counterparts. Finally, the uniqueness of the sibling study design allowed us to theorize probable

causes of the severe obesity as the siblings shared both genes and a previous home environment. We believe the most probable reason for the obesity is due to the interaction of behaviors with a nonshared genetic inheritance. It remains to be determined whether the development of obesity in only one of the two siblings is caused by differences in behavior or whether behavior changes as a result of obesity. Identification of genes related to the development of obesity would greatly aid in quantifying the effects of different behaviors on specific genetic backgrounds.

TABLE 1

Information About SF-36 Health Status Scales and the Interpretation of Low and High Scores

Concepts	No. of Items	Meaning of Scores: Low	Meaning of Scores: High
Physical functioning	10	Limited a lot in performing all physical activities including bathing or dressing	Performs all types of physical activities including the most vigorous without limitations due to health
Role limitations due to physical problems	4	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health, past 4 weeks
Social functioning	2	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical or emotional problems, past 4 weeks
Bodily pain	2	Very severe and extremely limiting pain	No pain or limitations due to pain, past 4 weeks
General mental health	5	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time, past 4 weeks
Role limitations due to emotional problems	3	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems, past 4 weeks
Vitality	4	Feels tired and worm out all of the time	Feels full of pep and energy all of the time, past 4 weeks
General health perceptions	5	Believes personal health is poor and likely to get worse	Believes personal health is excellent

TABLE 2

Social and Demographic Characteristics of Patients by Weight Status

	Severely Obese	Normal Weight	p-value
n	145	145	
BMI (kg/m^2)	44.7	24.4	<0.0001
age (yrs)	44.2 (10.0)	43.3 (11.9)	0.19
sex n (%)			
Female	97 (67)	92 (63)	0.54
Male	48 (33)	53 (37)	
Marial Status n %			
Married	103 (71)	114 (79)	0.14
Not Married	42 (29)	31 (21)	
Education n (%)			
<=High School	50 (34)	56 (39)	0.46
> High School	95 (66)	89 (61)	
Income Level			
<$15,000	14 (9)	13 (9)	0.07*
$15,000 - $24,999	20 (14)	14 (9)	
$25,000 - $49,999	68 (47)	52 (36)	
$50,000 or more	40 (28)	60 (42)	
retired	3 (2)	6 (4)	

Data are means (SD) unless otherwise noted.

*When comparing affected and unaffected income levels, the significance of a right-sided test is equal to 0.035 with more unaffected siblings making $50,000 than their affected siblings.

TABLE 3

Physiological and Emotional Well-Being: Differences Between Severely Obese and Normal Weight Siblings

	Affected	Unaffected	p value
	Mean (SD)	Mean (SD)	
Scale (n=)			
General (136)	57.2 (20.0)	77.6 (15.5)	<0.0001
Pain (136)	62.7 (19.8)	74.1 (18.5)	<0.0001
Emotion (145)	67.9 (46.8)	84.2 (36.1)	0.0012
Physical Functioning (145)	65.9 (27.2)	89.2 (16.6)	<0.0001
Role Physical (145)	62.5 (45.8)	89.1 (25.6)	<0.0001
Social (137)	75.9 (23.3)	87.2 (21.8)	<0.0001
Vitality (137)	42.5 (19.2)	61.2 (20.4)	<0.0001
Mental (136)	69.2 (19.8)	76.3 (13.7)	0.0008

SF-36 Scale Score:
0 = lowest possible score (poor health)
100 = highest possible score (good health)

TABLE 4

Nutrient Intake : Differences between SO (N=132) and NW (N=132) Siblings

	Severely Obese Mean(SD)**	Normal Weight Mean(SD)**	p-value
Total Calories (kcal)	2191.5 (876.7)	1824.2 (612.2)	<0.0001
Total Calories/body weight (kg)	16.9 (7.1)	26.2 (9.3)	<0.0001
Percent of Total Calories			
Fat	33 (6)	30 (7)	<0.0001
Animal Fat	19 (5)	17 (6)	<0.0001
Vegetable Fat	14 (5)	13 (4)	0.03
Saturated Fat	12 (3)	11 (3)	<0.0001
Monounsaturated Fat	12 (3)	11 (3)	<0.0001
Carbohydrate	50 (8)	53 (10)	0.0003
Protein	18 (4)	17 (3)	0.02
Animal Fat (gm)	47.7 (24.0)	33.8 (19.0)	<0.0001
Vegetable Fat (gm)	34.9 (17.9)	26.1 (13.5)	<0.0001
Saturated Fat (gm)	29.7 (14.6)	21.4 (10.4)	<0.0001
Monounsaturated Fat (gm)	31.4 (14.3)	22.2 (11.4)	<0.0001
Carbohydrates (gm)	269.9 (121.0)	242.8 (90.6)	0.02
Carbohydrates (gm)/Fat (gm)	3.7 (1.4)	4.6 (2.7)	<0.0001
Dietary Fiber (gm)	21.0 (8.9)	20.1 (9.0)	0.37
Protein (gm)	97.9 (37.6)	78.0 (28.9)	<0.0001
Caffeine (mg)	34.6 (19.1, 126.2)	34.7 (13.2, 196.8)	0.71*
Saccharin (mg)	2.1 (0.3, 27.2)	1.3 (0.03, 12.8)	0.05*
Alcohol (gm)	0.5 (-0.04, 0.9)	0.04 (0.3, 1.4)	0.23*
Cigarette years	0.01 (-0.02, 0.01)	0.008 (-0.02, 0.01)	0.84*

*Chi-Square Test
**For Chi-Squared Tests, data presented as Median (25th Quartile, 75th Quartile)

TABLE 5

Activity Level: Difference between Severely Obese and Normal Weight Siblings

	Severely Obese	Normal Weight	p-value
Caltrac Monitor	Mean (SD)**	Mean (SD)**	
N	134	134	
Total daily calories used	2007 (522)	1653 (563)	<0.0001
Total daily activity calories	590 (403)	575 (408)	0.75
Total daily calories used/kg body wt	15.7 (4.7)	23.2 (8.0)	<0.0001
Total daily activity calories/kg body wt	4.7 (3.4)	8.2 (5.8)	<0.0001
Activity Questionnaire			
N	144	144	
Number of times exercise/week	.2 (-4.0, 1.9)	1.4 (0.2, 3.2)	0.0002*
Blocks walked/day	3.2 (1.4, 8.0)	6.5 (2.6, 17.1)	<0.0001*
Walking Pace 1=strolling; 2=normal; 3=fairly brisk	1.9 (1.1, 2.1)	2.1 (1.9, 3.1)	<0.0001*
Flights climbed/day	2.8 (.1, 6.4)	6.2 (2.0, 10.5)	<0.0001*
View on physical activity 1 = I do enough physical activity 2 = I ought to do more	2.0 (2.0 , 2.0)	2.0 (1.0, 2.0)	<0.0001*
Level of exertion in exercise 2 = weak 3 = moderate 4 = somewhat strong 5 = Strong (heavy)	2.9 (1.7, 4.0)	4.0 (3.0, 5.6)	<0.0001*
Hours of vigorous activity/weekday	.2 (.008, .9)	1.0 (0.2, 1.7)	<0.0001*
Hours of vigorous activity/weekend	.4 (.07, 1.0)	1.1 (0.5, 2.2)	0.23*
Hours of moderate activity/weekday	2.1 (1.3, 4.8)	3.3 (1.8, 5.8)	0.05*
Hours of moderate activity/weekend	3.4 (1.9, 5.7)	4.6 (2.8, 6.6)	0.005*
Hours of light activity/weekday	5.9 (3.8 , 9.1)	6.0 (3.4, 8.8)	0.58*
Hours of light activity/weekend	4.1 (3.1, 6.1)	4.5 (3.1, 6.1)	0.91*
Hours spent sitting/weekday	5.1 (3.8, 7.8)	3.3 (2.2, 5.2)	<0.0001*
Hours spent sitting/weekend	5.3 (3.9, 7.8)	3.8 (2.5, 5.0)	0.91*
Hours spent sleeping/weekday	7.9 (6.9, 8.2)	7.8 (6.9, 8.1)	0.41*
Hours spent sleeping/weekend	8.0 (7.9, 8.9)	7.9 (6.9, 8.2)	0.009*

*Chi-Squared Test

**For Chi-Squared Tests, data presented as Median (25th Quartile, 75th Quartile)

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CHAPTER 5

Influence of Common Environmental Factors

on Families With and Without Aggregation of Severe Obesity[1]

[1]This chapter will be submitted for publication in Obesity Research

Influence of Common Environmental Factors on Families With and Without Aggregation of Severe Obesity

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ABSTRACT

Obesity, including severe obesity (BMI> or = 35 kg/m^2), is known to aggregate within families. This familial aggregation is suspected to be partially determined by shared genes. In order to further assess the combination of genes versus environment to severe obesity, this study uses a unique study design of aggregating and non-aggregating severely obese families. Aggregating defined families were required to have at least two severely obese siblings with one normal weight sibling (BMI < or = 27 kg/m2). Non-aggregating defined families were required to contain only one severely obese sibling and at least two normal weight siblings with all other first degree relatives meeting the normal weight criteria. The study design was based on the assumption that aggregating families have a greater genetic influence for the development of obesity and non-aggregating families have limited genetic inheritance. Environmental influences, including health-related quality of life issues, nutrient intake and physical activity, were examined in order to assess genetics versus environment in these two types of families. All participants completed the standardized and validated SF-36 health status questionnaire, a semi-quantitative food frequency questionnaire, a physical activity questionnaire, as well as study-specific questionnaires on weight loss history and socioeconomic status. Caltrac accelerometers were worn for 3 consecutive days by all subjects to assess daily activity expenditure. In addition to statistical comparison of aggregating affected to non-aggregating affected subjects and aggregating unaffected to non-aggregating unaffected subjects, the mean intrapair difference of an aggregating affected and unaffected sibship was compared to the mean intrapair difference of a non-aggregating affected and unaffected sibship. Results showed essentially no difference in environmental factors between the aggregating and non-aggregating affected, as well as the mean intrapair differences between aggregating and non-aggregating sibships as previously described.

Comparative results of the unaffected showed the aggregating normal weight subjects had a greater weight-adjusted total caloric intake and activity expenditure (weight-adjusted) than the non-aggregating normal weight subjects. From these results, we have concluded there is little difference in the environmental influences affecting the aggregating and non-aggregating families suggesting that the underlying genetic contribution to severe obesity in these two family types is also similar.

INDEX TERMS: Obesity, Genetic, Environmental, Familiality, SF-36, Quality of Life, Physical Activity, Nutrient Intake, Body Weight, Body Mass Index

INTRODUCTION

A number of published research studies have explored the environmental and genetic influence on obesity (1,2,5,8) and found both genes and shared environment can endow members of a family with a predisposition to obesity. These studies suggest genes may determine who is susceptible to becoming obese and that environment determines the extent of obesity in vulnerable individuals. These studies further conclude that severe obesity most likely results from the accumulation of environmental factors over time in genetically susceptible persons.

Despite above findings, limited research has examined common behavorial influences such as emotional and physical well-being, physical activity and dietary intake in relation to the degree of family aggregation of obesity. In a previous study, our group compared biochemical and anthropometric variables of severely obese probands selected from families where two or more first degree family

members were severely obese with probands who were the only severely obese person in their immediate family (See Appendix 11). We found no significant differences in biochemical and anthropometric variables between probands representing families aggregating and not aggregating for severe obesity, raising the question regarding the extent environmental influences might have on the degree of obesity present in these two family types. To explore this question, this study focused on quality of life perception, physical activity and dietary intake of both severely obese and normal weight siblings representing families aggregating and not aggregating for severe obesity.

METHODS

Subjects

All severely obese (affected) individuals in this study met the criteria for severe obesity, defined as a body mass index (BMI) of 35 kg/m^2 or greater. We found a BMI of 35 kg/m^2 was on average approximately 75 pounds over ideal body weight when ideal weight was determined from the Metropolitan Life Insurance Tables of 1983 using elbow breadth, or using the medium frame and midpoint weight range when clinic data were not available. All unaffected participants met the criteria for normal weight, which we defined as a BMI of 27 kg/m^2 or less for both men and women. This normal weight upper limit is approximately 30 pounds over ideal body weight (18,19).

Aggregating/Non-Aggregating Study Design

Families were recruited for participation in our study based upon the number of first degree relatives with severe obesity. Families with aggregating severe obesity

were required to have at least two severely obese siblings with one normal weight sibling. Non-aggregating defined families were required to contain only one affected sibling with all other first degree relatives normal weight, and at least two normal weight siblings. Ninety-two aggregating sibships (2 siblings severely obese; 1 sibling normal weight) and 53 non-aggregating sibships (1 sibling severely obese; 2 sibs normal weight) participated in the study.

Recruitment of Subjects

Subjects were recruited from two sources. The first source was identified from a population-based family history database of over 100,000 families. Data were collected from Health Family Tree questionnaires which are detailed family histories completed by high school students and their parents as part of the Utah school curriculum (6, 25). There is little difference in participation rates between schools in rural versus urban areas or between high and low income areas. Health information reported by the families includes the report of "usual weight" categorized as: slender or average; 10-49 pounds overweight; 50-99 pounds overweight; or over 100 pounds overweight.

From the 100,000 family history population-based database, over 4,000 morbidly obese probands and their siblings were initially identified. Of these 4,000 families with one or more morbidly obese members, 290 were potential familial MO families and 487 were potential nonfamilial MO families.

All nonfamilial MO families (487) and a random sample of familial MO families (97) were sent introductory letters (See Appendix 2) and then contacted by telephone to verify the Health Family Tree record and to ascertain their interest as a participant in the study.

Following verification, 440 of the 487 potential nonfamilial MO families and 26 of the 97 potential and randomly selected familial MO families did not meet the

defined criteria for these two types of MO families. Therefore, 47 of the nonfamilial MO families and 71 of the familial MO families were identified from the population-based family history database.

The second source of subjects were participating in a very-low-calorie diet, weight-loss program (Optifast, Sandoz Nutrition) operating at 4 different hospitals in Utah. The directors of the respective weight-loss clinics obtained permission from program participants prior to their being contacted for research participation. Individuals giving consent were then recruited by telephone. From this source, 6 nonfamilial MO families and 22 familial MO families were identified.

Data Collection

This research study was approved by the Institutional Review Board at the University of Utah, and individuals gave written consent prior to participation. Data collection took place over a 36-month period from January 1994 through December 1996 at the Cardiovascular Genetics Research Clinic, University of Utah. Questionnaires were distributed to obtain data for the following environmental variables: anthropometrics (current height, current weight, greatest weight, age at greatest weight), SF-36 health-related quality of life values measuring physiological and emotional well-being, dietary intake, energy expenditure, alcohol intake, cigarette use, medication use, weight history, weight loss history, pregnancy history, socioeconomic status, and education level.

In addition to all subjects receiving and completing above mentioned questionnaires, each member of the sibship was given a Caltrac activity monitor (Muscle Dynamics Fitness Network, Torrance, CA). The Caltrac was fixed to the trunk of the body to measure acceleration of the trunk during physical activity. Each Caltrac microcomputer was programmed with the subject's age, height,

weight and gender. The participants were asked to wear the Caltrac accelerometer for 3 consecutive days and to record their total daily energy expenditure (measured in kcal) and their activity expenditure (measured in kcal) at the end of each day (just prior to going to bed), and first thing in the morning. With the measures taken in the evening and morning we were able to calculate daily caloric expenditure values for three consecutive days. The monitor was mailed back after wearing the monitor for three days. One hundred percent of the subjects included in the activity expenditure analysis wore the monitor for 1 full day. Ninety six percent wore the Caltrac for 2 days and 92% wore the monitor for the complete 3 day period.

Data for the three areas of behavioral influences (physical activity, dietary intake and emotional/mental well-being) were collected in 145 sibships (92 aggregating sibships and 53 non-aggregating sibships). The activity questionnaire was completed by 92 aggregating sibships and 53 non-aggregating sibships. Nutrition information was completed by 81 aggregating sibships and 50 non-aggregating sibships. Eighty-nine aggregating sibships and 51 non-aggregating sibships completed the SF-36 form. The Caltrac activity monitor data were complete for 83 aggregating sibships and 50 non-aggregating sibships.

Total caloric intake and energy expenditure values were divided by weight in kilogram to adjust for differences in weight. A weight adjustment provides more comparable values as energy intake and expenditure are highly related to body size. Furthermore, as some individuals tend to generally under- or overestimate their food intake, nutrient intake values for total fat, animal fat, vegetable fat, saturated fat, monounsaturated fat, carbohydrate and protein were calorie-adjusted to compare as proportions in addition to absolute amounts.

Instruments

Physical Activity Questionnaire

Physical activity questions were taken from the validated and standardized physical activity questionnaire designed by Paffenbarger and colleagues (9,10). The physical activity questions were qualitative concerning such items as: attitudes on physical activity, number of exercise sessions per week, blocks walked or flights climbed per day, usual pace of walking and level of exertion in exercise. The final section of the questionnaire required the participants to estimate the hours of an average weekday and weekend by activity type (sleeping, sitting, light activity, moderate activity, and vigorous activity).

SF-36 Questionnaire

The 36-item short-form (SF-36) was designed to survey health status in the Medical Outcomes Study (MOS), a four-year observational study designed to examine the influence of specific characteristics of providers, patients and health systems on outcomes of care (17). The SF-36 addresses general health concepts not specific to any age, disease or treatment group. It measures perceptions regarding basic human experiences such as functional status, emotional well-being and overall health. The SF-36 was standardized in 1992, and has been used in many studies. It has been proven to be as reliable, consistent, reproducible and as valid as longer health status instruments. The popularity of SF-36 appears to be largely driven by its brevity, yet completeness (20). It provides a yardstick for health status comparisons in subjects with the same clinical condition and between subjects with different clinical conditions.

The SF-36 assesses eight health concepts: (1) limitations in physical activities because of health problems; (2) limitations in social activities because of physical

or emotional problems; (3) limitations in usual role activities because of physical health problems; (4) bodily pain; (5) general mental health (psychological distress and well-being); (6) limitations in usual role activities because of emotional problems; (7) vitality (energy and fatigue); and (8) general health perceptions (20). Definitions of each scale are listed in Table 1. Thus, the SF-36 is a generic, self-completion health status questionnaire which contains 36 items, analyzed as 8 scales and a one-item measure of change in health. The possible range of the SF-36 scale scores are 0 to 100, with zero indicating the lowest possible score (poor health), and 100 the highest possible score (good health). A score is calculated for each of the areas by summing responses to individual items and using a scoring algorithm converting to a scale from 0 to 100. Using the scoring algorithms as suggested by its developers (21) permits comparisons with published Medical Outcomes Study results and national norms.

(See Table 1)

Willett Food Frequency Questionnaire

A 61-item semiquantitative food frequency questionnaire was used to obtain estimated nutrient intake (7,12,13,22,23). Validation studies indicate that the semi-quantitative food frequency questionnaire is remarkably robust (7,12,13,22,23). The questionnaire consists of two components: a list of foods; and a set of frequency-of-use response categories. The aim of the food frequency questionnaire is to assess the frequency with which certain food items or food groups are consumed during a specified time period (i.e., daily, weekly, monthly, yearly). The fact that this questionnaire is also semiquantitative means that it attempts to quantify usual portion sizes of the food items of interest. Nutrient content is computed by multiplying the relative frequency that each food item is

consumed by the nutrient content of the average portion size, and then multiplying by the number of portions.

Statistical Analysis

Means and standard deviations were calculated to describe the basic characteristics of the patient population. Prior to statistical analysis of the remaining variables, the significance level was set to 0.01 to correct for five multiple comparisons (diet, physical activity, smoking years, physical functioning, and emotional well-being). Using data from all three siblings, variables were adjusted for age and sex in a general linear model (GLM, 14). Following age and sex adjustment, one of the two affected (severely obese) aggregating sibs was randomly selected and paired to the remaining unaffected aggregating sib, and one of the two unaffected (normal weight) non-aggregating sibs was randomly selected and paired with the remaining affected sib. This pairing method facilitated comparison of aggregating versus non-aggregating sibships. Within the general linear model, two-sample t-tests on the age- and sex-adjusted residuals were used for assessing differences in environmental variables between aggregating and non-aggregating severely obese individuals, between aggregating and non-aggregating normal weight individuals and for determining whether mean intrapair differences were significant between affected and unaffected siblings in non-aggregating and aggregating families. A two-sample t-test was then used to test for differences in the aggregating and non-aggregating intrapair differences. For categorical variables or variables not normally distributed, comparisons were calculated with a McNemars, Chi-squared or Wilcoxon rank sum test.

RESULTS

Social/Demographic Characteristics

Table 2 details age, BMI, gender distribution and social/demographic characteristics of the patient population by family type and affected status. The BMI of affected siblings was greater than the normal weight siblings in both aggregating (BMI difference: 20.2 kg/m^2; p-value<0.0001) and non-aggregating (BMI difference: 20.4 kg/m^2; p-value<0.0001) severe obesity families. Aggregating affected subjects had a higher BMI than non-aggregating affected subjects (BMI difference: 3.0 kg/m^2; p-value= 0.007). Likewise, the BMI of aggregating unaffected participants was greater than the BMI of non-aggregating unaffected participants(BMI difference: 3.2 kg/m^2; p-value<0.0001). Non-aggregating affected siblings were older than their normal weight siblings (age difference: 3.9 years; p-value=0.03). A larger proportion of the affected individuals were female in the non-aggregating MO families than in the aggregating MO families (percent female difference: 17%; p-value<0.05). Marital status and education levels did not differ significantly.

(SeeTable 2)

Aggregating versus Non-aggregating Severely Obese Subjects

The comparisons of environmental variables between the aggregating and non-aggregating severely obese subjects are detailed in Tables 3, 4 and 5. Of the 49 variables tested, only saccharin intake differed: mean saccharin intake was 14.8 mg higher in the non-aggregating obese participants (p=0.01)(See Table 3). Other differences that approached significance included: percent of dietary vegetable fat, caffeine intake and the number of flights of stairs climbed per day. Non-

aggregating obese participants reported a 2% higher vegetable fat intake and a 26.7 milligram higher caffeine intake than the aggregating obese (p=0.03; p=0.03) (See Table 3). Non-aggregating severely obese subjects reported walking faster (p=0.04) and exercising more per week than the aggregating severely obese subjects (p=0.04)(See Table 4).

(See Tables 3, 4, and 5)

Aggregating versus Non-aggregating Normal Weight Subjects

Tables 6, 7 and 8 show the comparisons between aggregating and non-aggregating normal weight participants. Both weight-adjusted total caloric intake and activity expenditure (weight-adjusted) were lower in the aggregating unaffected participants than the nonaggregating counterparts (caloric intake: 6.7 kcal/kg difference ($p<0.0001$); activity expenditure: 4.1 kcal/kg differences (p=0.009)) (See Table 6 and 7). Consumption of animal fat was somewhat lower in the aggregating normal weight subjects (6.3 gm lower; p=0.04). Non-aggregating participants spent fewer hours sitting on the weekend and this difference approached significance (0.6 fewer hours; p=0.03).

(See Tables 6, 7 and 8)

Mean Intrapair Difference between Aggregating and Nonaggregating Affected and Unaffected Siblings

Mean intrapair differences between aggregating and nonaggregating affected and unaffected siblings are reported in Tables 9, 10 and 11. Of the 49 variables tested, none were different at the 0.01 alpha level. Percent dietary vegetable fat and saccharin intake were somewhat different. In non-aggregating obesity

families, the mean intrapair difference was higher for percent dietary vegetable fat (2.4% higher; p=0.02) and saccharin intake (2.1 mg higher; p=0.03) (See Table 9).

(See Tables 9, 10 and 11)

DISCUSSION

Bouchard has previously equated specific phenotypes associated with obesity as the sum of three factors: genetic, environmental and genetic/environmental interaction (2). To determine the degree of influence each of these specific factors play in obesity is complex, and is even further complicated by the heterogeneous nature of obesity. As a result, several methodological strategies, including twin and adoptive studies as well as large pedigree studies, have been undertaken to further define the genetic, environmental and interactive influences on obesity (1,2,3,4,5,8,11,15,16,24).

In an effort to reduce the heterogeneity of obesity and further isolate the genetic aspect of this disorder, we chose to focus on severe obesity (severe obesity occurs in less than 5% of the general population) and to then identify families where aggregation for severe obesity was and was not present in order to compare affected and nonaffected siblings raised together in both family types. Using this study design we chose a hypothesis that suggested families aggregating for severe obesity have a greater genetic influence (and perhaps less environmental influence) for this disorder and that severe obesity in families where only one first-degree relative is affected is likely to be more environmentally caused. Further, using this hypothesis we assumed the intrapair differences of the environmental variables between affected and unaffected siblings would be significantly greater in the non-aggregating families when compared to the aggregating families, supporting

further the notion of a stronger environmental influence on the one and only affected sibling in non-aggregating families with a greater underlying genetic influence on the aggregating family sibships.

To test the hypothesis, initial comparison was made between environmental measurements of the aggregating and non-aggregating affected members (severely obese participants). The assumption was that the non-aggregating affected subjects would have a greater environmental influence when compared to the more genetically-influenced, aggregating affected subjects. Prior to statistical analysis, the significance level was set to 0.01 for five multiple comparisons (diet, physical activity, cigarette smoking, emotional well-being and physiological functioning). At this significance level, of the 49 environmental factors, only saccharin intake differed between aggregating and non-aggregating severely obese subjects. Saccharin intake was higher in the non-aggregating severely obese subjects when compared to aggregating severely obese subjects.

As previously discussed, in an effort to assess whether stronger environmental influences effected the single severely obese sibling in the non-aggregating families in comparison to the aggregating family sibships, mean intrapair differences were examined between affected and unaffected siblings in aggregating and non-aggregating severely obese families. If it is assumed that the aggregating severe obesity is genetically caused, affected and unaffected siblings could potentially have the same environmental risk factor profile, yet only the gene carrier becomes obese. Non-aggregating obesity was hypothesized to be environmentally caused predicting significantly different environmental risk factor profiles in non-aggregating affected and unaffected siblings. If these assumptions were true, we would have hoped to differentiate the extent of environmental influence contributing to severe obesity in these two family types. However, mean intrapair differences did not differ between affected and unaffected siblings

belonging to aggregating and non-aggregating severely obese families.

Final comparison was made between the normal weight siblings in aggregating and non-aggregating severely obese families. In aggregating obesity, the severely obese siblings are assumed to have received a genetic predisposition to obesity while the normal weight siblings are assumed to have not received such a genetic tendency to gain weight. Accordingly, it is assumed that both the aggregating and non-aggregating unaffected siblings have no genetic tendency towards obesity. Thus, aggregating and non-aggregating unaffected siblings would not be expected to differ environmentally. In comparing aggregating and non-aggregating normal weight participants, only weight-adjusted total caloric intake and activity calories (weight-adjusted) were significantly different at the 0.01 alpha level. The significance of the weight-adjusted values were most likely due to over-adjusting for body weight differences in the normal weight subjects (non-aggregating unaffected participants weighing significantly less than the aggregating unaffected counterparts). A lean body mass adjustment (value not obtained) would have been preferable for body-size associated variables (e.g. caloric intake and activity expenditure).

With 92 familial and 53 nonfamilial sibships, the previously detailed statistical comparisons had 82% power to detect a significant difference of 0.50 standard deviation at a p-value of 0.05. However, after adjusting for 5 independent, multiple comparisons (alpha = 0.01), power to detect a significant difference reduced to 0.6 standard deviation. Comparative mean differences (adjusted for the pooled standard deviations) were very small (average difference was approximately 0.01) (See Appendix), and thus not scientifically meaningful. As there were few important differences, the issue of power became less concerning. Therefore, this study design had power to detect scientifically important differences, but not enough power to detect small and clinically

irrelevant differences.

Previous to this study's findings, our group examined the question of whether or not anthropometric and biochemical measures of severely obese subjects were expressed differently in aggregating and non-aggregating severely obese subjects (See Appendix 11). The central question asked was whether or not the mechanism for the development of severe obesity is the same in aggregating versus non-aggregating severely obese families. If it is assumed that aggregating families have a genetic predisposition to environmental insults, then one might expect different biochemical or anthropometric profiles between the groups, hinting at an underlying mechanism. On the other hand, it can be argued that the non-aggregating families are merely those families who might have a genetic predisposition but only one sibling inherited the gene. Blood pressure, as well as a number of anthropometric and biochemical variables were measured, including percent body fat, insulin, blood lipids and urine catecholamines. Based upon statistical comparison of the two severe obesity groups, there were no significant differences between aggregating and non-aggregating severely obese probands in anthropometric or biochemical measurements (to be submitted for publication).

The virtual similarity between aggregating and non-aggregating severely obese subjects would suggest that regardless of the reason for weight gain, the gross physiologic reponse to that weight gain appears to be similar among groups. These findings suggest that the biochemical and physiological characteristics related to severe obesity are the same for aggregating and non-aggregating severely obese subjects. These findings lead our group to hypothesize concerning possible environmental differences in aggregating and non-aggregating severely obese families. However, the environmental hypothesis was found to be unsubstantiated, leading us to wonder about a similar genetic influence for severe obesity in both aggregating and non-aggregating severely obese subjects. This being the case,

further expansion of the non-aggregating families (beyond the first-degree relatives) should reveal the presence of significant aggregation for severe obesity in the extended pedigree. These results would then suggest there are few, if any, truly non-aggregating severely obese families.

This is an important finding. If non-aggregating severely obese families do not exist, or are in the least very rare, then studies looking for obesity-related genetic effects using positive and negative family histories may incorrectly classify pedigree-related data and significantly bias scientific findings. For these reasons, further effort to expand family pedigrees initially identified as non-aggregating becomes a very important methodological consideration.

Because this study was a cross-sectional study, cause versus effect of severe obesity could not be determined. For example, whether dietary habits differed between aggregating and non-aggregating affected subjects prior to or during weight gain and then became similar when severe obesity status was reached is uncertain. However, self-reported age-of-obesity onset for both aggregating and non-aggregating SO subjects occurred between the ages of 20 and 21 ($p=0.97$). Because affected subjects from both family types were apparently gaining weight during comparable periods of their lives, we may assume environmental influences during this time were similar for each group.

Conceptually, misclassifying sibships into aggregating or non-aggregating SO families may have occurred as a result of study design where family inclusion only required three siblings. A more stringent criteria for non-aggregating SO would have required the affected subject to be the one and only one SO person among first degree relatives, with at least four other normal weight siblings. In actuality, this study approached this more stringent methodology in that the average non-aggregating family equaled 5.0 siblings and the average aggregating family was 6.7 siblings, not significantly different. Further, given the criterion of less than 27

kg/m^2 for normal weight and greater than 35 kg/m^2 for SO (8 kg/m^2 difference), if non-aggregating siblings were misclassified as normal weight sibs when in reality they were over the 27 kg/m^2 cutpoint, the entire family would have been disqualified rather than reclassified as an aggregating SO family.

In summary, the contribution of environmental factors to severe obesity status did not differ between aggregating and non-aggregating severely obese subjects. Furthermore, environmental variables between the aggregating SO and normal weight sibs and non-aggregating SO and normal weight sibs were not significantly different. Finally, using this unique family study design, we anticipated a stronger underlying genetic influence on the aggregating SO sib and a greater environmental impact upon the non-aggregating SO sib. With little difference found between these two family types it was concluded: 1) genetic differences between aggregating and non-aggregating families are likely small; and 2) environmental factors included in this study are believed to operate similarly within the two family types.

TABLE 1

Information About SF-36 Health Status Scales and the Interpretation of Low and High Scores

Concepts	No. of Items	Meaning of Scores	
		Low	High
Physical functioning	10	Limited a lot in performing all physical activities including bathing or dressing	Performs all types of physical activities including the most vigorous without limitations due to health
Role limitations due to physical problems	4	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health, past 4 weeks
Social functioning	2	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical or emotional problems, past 4 weeks
Bodily pain	2	Very severe and extremely limiting pain	No pain or limitations due to pain, past 4 weeks
General mental health	5	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time, past 4 weeks
Role limitations due to emotional problems	3	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems, past 4 weeks
Vitality	4	Feels tired and worm out all of the time	Feels full of pep and energy all of the time, past 4 weeks
General health perceptions	5	Believes personal health is poor and likely to get worse	Believes personal health is excellent

TABLE 2

Social and Demographic Characteristics of Patients by Family Type and Affected Status

	Aggregating		Non-Aggregating	
	Affected	Unaffected	Affected	Unaffected
n	182	91	54	105
BMI	45.7 (6.9)ac	25.5 (3.1)ad	42.7 (5.8)bc	22.3 (2.2)bd
Weight (kg)	134.5 (23.6)eg	75.4 (9.4)fg	124.8 (16.4) eh	65.6 (7.2)fh
age (yrs)	44.1 (13.0)	43.3 (13.4)	45.2 (8.5)i	41.3 (11.4)I
sex n (%)				
Male	78 (43)j	40 (44)	14 (26)j	38 (36)
Female	104 (57)	51 (56)	40 (74)	67 (64)
Marial Status n (%)				
Married	137 (75)	70 (77)	39 (72)	77 (73)
Divorced/ Separated	16 (9)/0	9 (10)/0	6 (11)/ 1(2)	9 (9)/ 1 (1)
Single	20 (11)	9 (10)	7 (13)	16 (15)
Widowed	7 (4)	3 (3)	1 (2)	2 (2)
Not Marked	4 (2)	0	0	2 (2)
Education n (%)				
<=High School	66 (36)	37 (41)	17 (32)	38 (36)
> High School	116 (64)	54 (59)	37 (68)	67 (64)

Data are means (SD) unless otherwise noted.
Means with different superscripts are significantly different ($p<0.05$).

TABLE 3

Dietary Intake: Aggregating versus Non-Aggregating Severely Obese Probands

Dietary Intake	Aggregating Mean (SD) [n=85]	Non-Aggregating Mean (SD)[n=52]	p-value
Total Calories (kcal)	2158.1 (1019.0)	2182.1 (630.3)	0.87
Total Calories (kcal)/Body Weight (kg)	16.3 (7.7)	17.8 (5.6)	0.21
Percent of Total Calories			
Total Fat	32 (7)	34 (6)	0.14
Animal Fat	19 (6)	19 (5)	0.69
Vegetable Fat	13 (4)	15 (6)	0.03
Saturated Fat	12 (3)	12 (3)	0.36
Monounsaturated Fat	12 (3)	13 (3)	0.27
Carbohydrate	50 (9)	49 (8)	0.47
Protein	18 (4)	18 (3)	0.80
Animal Fat (gm)	46.4 (25.3)	45.3 (18.1)	0.77
Vegetable Fat (gm)	32.3 (20.0)	36.3 (15.3)	0.19
Saturated Fat (gm)	28.5 (16.2)	29.0 (10.0)	0.82
Monounsaturated Fat (gm)	29.8 (16.1)	30.8 (10.2)	0.67
Carbohydrates (gm)	270.7 (138.9)	271.6 (92.7)	0.96
Dietary Fiber (gm)	21.0 (9.5)	21.6 (9.1)	0.71
Carbohydrates (gm)/Fat (gm)	3.8 (1.5)	3.5 (1.3)	0.25
Protein (gm)	96.2 (41.9)	97.8 (31.2)	0.80
Caffeine (mg)	27.7 (1.3, 7.7)	54.4 (24.4, 129.7)	0.03*
Saccharin (mg)	1.5 (-0.2, 13.5)	5.7 (1.2, 77.6)	0.01*
Alcohol (gm)	0.4 (-0.5, 0.9)	0.6 (-0.1, 0.9)	0.31*
Cigarette Years	.009 (-0.02, 0.01)	0.01 (0.006, 0.01)	0.39*

N=92/53 for Familial/Nonfamilial Cigarette Years
*Wilcoxon Rank Sum Test
**For Chi-Squared Tests, data presented as Median (25th Quartile, 75th Quartile)

TABLE 4

Physical Activity: Aggregating versus Non-Aggregating Severely Obese Probands

Physical Activity	Aggregating Mean (SD)**	Non-Aggregating Mean (SD)**	p-value
Caltrac	[N=89]	[N=52]	
Total Calories Used	2,006 (521)	2016 (516)	0.76
Total Activity Calories	566(407)	653 (388)	0.21
Total Calories Used/Body Weight (kg)	15.3 (4.8)	16.6 (4.6)	0.10
Total Activity Calories/Body Weight (kg)	4.5 (3.5)	5.4 (3.3)	0.12
Questionnaire	[N=92]	[N=53]	
Blocks/day	2.9 (1.3, 7.7)	3.5 (2.0, 9.0)	0.27*
Usual Pace of Walking (1=strolling; 2=normal)	1.8 (1.1, 2.1)	1.9 (1.1, 2.1)	0.04*
Flights/day	2.7 (1.0, 6.1)	3.8 (1.8, 7.5)	0.20*
Number Times Exercise/week	0.2 (-0.03, 1.6)	0.4 (0.1, 2.0)	0.04*
Exertion Level in Exercise (2=weak; 3=moderate)	2.7 (1.7, 4.0)	3.1 (1.7, 4.1)	0.62*
View of Physical Activity	2.0 (2.0, 2.0)	2.0 (2.0, 2.0)	0.35*
Hours of Sleep/weekday	7.9 (6.9, 8.2)	7.9 (6.9, 8.1)	0.46*
Hours of Sleep/weekend	8.1 (7.9, 9.0)	8.0 (7.9, 8.9)	0.67*
Hours of Sitting/weekday	5.3 (3.7, 7.8)	5.1 (3.8, 7.1)	0.70*
Hours of Sitting/weekend	5.1 (3.7, 7.8)	5.7 (4.1, 8.1)	0.27*
Hours of Light Activity/weekday	5.9 (3.8, 8.6)	6.2 (3.9, 9.9)	0.82*
Hours of Light Activity/weekend	4.1 (3.1, 6.1)	4.1 (2.8, 6.1)	0.26*
Hours of Moderate Activity/weekday	2.1 (1.3, 4.8)	2.1 (1.2, 5.9)	0.81*
Hours of Moderate Activity/weekend	3.0 (1.8, 4.9)	3.7 (2.4, 5.9)	0.24*
Hours of Vigorous Activity/weekday	0.1 (-0.02, 1.0)	0.2 (0.1, 0.9)	0.24*
Hours of Vigorous Activity/weekend	0.4 (-0.02, 1.2)	0.4 (0.2, 0.7)	0.93*

*Wilcoxon Rank Sum Test

**For Chi-Squared Tests, data presented as Median (25th Quartile, 75th Quartile)

TABLE 5

Physiological and Emotional Well-Being: Aggregating versus Non-Aggregating Severely Obese Probands

SF-36	Aggregating Mean (SD)	Non-Aggregating Mean (SD)	p-value
N	92	53	
General Health	53.2 (21.3)	56.2 (20.8)*	0.42
Physical Pain	61.1 (19.0)	65.1 (21.2)*	0.25
Emotional Functioning	70.9 (36.7)	68.8 (47.1)	0.78
Physical Functioning	60.8 (22.7)	66.3 (26.1)	0.18
Role Physical	59.8 (40.8)	61.0 (46.5)	0.87
Social	73.1 (26.5)	75.6 (22.2)*	0.54
Vitality	42.7 (19.7)	39.1 (20.2)*	0.31
Mental	68.5 (20.7)	68.5 (21.1)*	0.99

*N=51 for the following Nonfamilial SF-36 variables: General Health, Physical Pain, Social, Vitality, and Mental

SF-36 Scale Score:
0 = lowest possible score (poor health)
100 = highest possible score (good health)

TABLE 6

Dietary Intake: Aggregating versus Non-Aggregating Normal Weight Siblings

	Aggregating Mean (SD) [n=87]**	Non-Aggregating Mean (SD)[n=52]**	p-value
Dietary Intake			
Total Calories (kcal)	1774.3 (639.4)	1955.7 (592.0)	0.10
Total Calories (kcal)/Body Weight (kg)	23.7 (8.3)	30.4 (9.9)	<0.0001
Percent of Total Calories			
Total Fat	29 (8)	30 (7)	0.62
Animal Fat	16 (6)	17 (6)	0.30
Vegetable Fat	13 (4)	13 (5)	0.58
Saturated Fat	11 (3)	11 (3)	0.64
Monounsaturated Fat	11 (3)	11 (3)	0.54
Carbohydrate	54 (11)	53 (9)	0.57
Protein	17 (3)	18 (4)	0.68
Animal Fat (gm)	31.9 (16.9)	38.2 (17.7)	0.04
Vegetable Fat (gm)	26.0 (13.4)	27.3 (11.9)	0.57
Saturated Fat (gm)	20.7 (10.2)	23.6 (9.6)	0.10
Monounsaturated Fat (gm)	21.3 (10.9)	24.4 (8.5)	0.07
Carbohydrates (gm)	237.5 (95.8)	256.0 (84.0)	0.25
Dietary Fiber (gm)	19.9 (9.9)	19.8 (6.9)	0.92
Carbohydrates (gm)/Fat (gm)	4.8 (2.8)	4.4 (2.5)	0.43
Protein (gm)	75.4 (28.5)	84.3 (29.4)	0.08
Caffeine (mg)	27.4 (13.2, 224.3)	47.5 (14.3, 178.6)	0.81*
Saccharin (mg)	2.2 (-0.4, 23.1)	0.7 (-0.3, 2.4)	0.10*
Alcohol (gm)	0.3 (-0.4, 1.7)	0.5 (-0.2, 1.2)	0.68*
Cigarette Years	0.006 (-0.02, 0.01) [92]	0.01 (-0.001, 0.01)	0.06*

N=92 for Aggregating Cigarette Years
*Wilcoxon Rank Sum Test
**For Chi-Squared Tests, data presented as Median (25th Quartile, 75th Quartile)

TABLE 7

Physical Activity: Aggregating versus Non-Aggregating Normal Weight Siblings

Physical Activity	Aggregating Mean (SD)	Non-Aggregating Mean (SD)	p-value
Caltrac			
N	85	52	
Total Calories Used	1,716 (598)	1,539 (470)	0.06
Total Activity Calories	590 (533)	636 (392)	0.15
Total Calories Used/Body Weight (kg)	22.9 (7.9)	23.6 (8.0)	0.64
Total Activity Calories/Body Weight (kg)	5.7 (5.4)	9.8 (6.0)	0.009
Questionnaire			
N	92	52	
Blocks/day	8.1 (2.9, 20.2)	5.5 (2.3, 13.9)	0.31*
Usual Pace of Walking (2=normal; 3=fairly brisk)	2.1 (1.9, 3.1)	2.1 (1.9, 3.1)	0.78*
Flights/day	6.2 (2.0, 10.6)	5.4 (2.0, 10.4)	0.95*
Number Times Exercise/week	1.1 (0.2, 3.1)	2.0 (0.2, 3.3)	0.33*
Exertion Level in Exercise (4=somewhat strong) (5=strong (heavy)	4.1 (3.0, 5.5)	3.9 (2.9, 5.9)	0.87*
View of Physical Activity (1=I do enough; 2=should do more)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	0.06*
Hours of Sleep/weekday	7.8 (6.9, 8.1)	7.9 (6.9, 8.1)	0.82*
Hours of Sleep/weekend	7.9 (7.0, 8.2)	7.9 (6.9, 8.9)	0.53*
Hours of Sitting/weekday	3.6 (2.2, 6.0)	3.2 (2.2, 4.8)	0.57*
Hours of Sitting/weekend	3.9 (2.7, 5.4)	3.3 (2.2, 4.4)	0.03*
Hours of Light Activity/weekday	6.2 (3.2, 8.7)	5.9 (3.8, 9.1)	0.78*
Hours of Light Activity/weekend	4.1 (2.5, 6.1)	4.8 (3.1, 7.1)	0.35*
Hours of Moderate Activity/weekday	3.1 (1.5, 5.9)	3.8 (1.9, 5.8)	0.47*
Hours of Moderate Activity/weekend	4.2 (2.6, 6.6)	5.2 (3.6, 6.5)	0.07*
Hours of Vigorous Activity/weekday	0.8 (0.1, 1.6)	1.1 (0.2, 1.9)	0.13*
Hours of Vigorous Activity/weekend	1.0 (0.5, 1.8)	1.4 (0.6, 2.3)	0.08*

*Wilcoxon Rank Sum Test

**For Chi-Squared Tests, data presented as Median (25th Quartile, 75th Quartile)

TABLE 8

Physiological and Emotional Well-Being: Aggregating versus Non-aggregating Normal Weight Siblings

	Aggregating Mean (SD) [n=]	Non-Aggregating Mean (SD)[n=]	p-value
SF-36			
General Health	77.1 (15.1) [89]	80.2 (19.1) [52]	0.33
Physical Pain	72.9 (19.1) [89]	76.7 (18.8) [52]	0.25
Emotional Functioning	81.0 (41.2) [92]	84.2 (36.8) [53]	0.64
Physical Functioning	87.6 (16.8) [92]	89.1 (26.5) [53]	0.72
Role Physical	90.4 (23.1) [92]	83.6 (37.3) [53]	0.23
Social	85.9 (23.3) [90]	88.9 (20.2) [52]	0.44
Vitality	61.7 (18.6) [90]	64.6 (22.2) [52]	0.43
Mental	75.0 (14.6) [89]	78.8 (11.3) [52]	0.08

SF-36 Scale Score:
0 = lowest possible score (poor health)
100 = highest possible score (good health)

TABLE 9

Mean Intrapair Dietary Intake Differences of Aggregating and Non-Aggregating Severely Obese and Normal Weight Sibs

Dietary Intake	Aggregating Mean (SD) [n=81]	Non-Aggregating Mean (SD)[n=50]	p-value
Total Calories (kcal)	416.2 (1096.1)	240.6 (800.7)	0.29
Total Calories (kcal)/Body Weight (kg)	-7.0 (10.2)	-9.1 (10.4)	0.26
Percent of Total Calories			
Total Fat	3 (8)	3 (8)	0.93
Animal Fat	3 (7)	0.5 (8)	0.07
Vegetable Fat	0.2 (5)	3 (6)	0.02
Saturated Fat	1 (3)	0.7 (4)	0.47
Monounsaturated Fat	1 (4)	1 (3)	0.83
Carbohydrate	-3 (11)	-3 (10)	0.74
Protein	0.9 (4)	0.1 (4)	0.31
Animal Fat (gm)	14.4 (28.5)	5.9 (27.9)	0.09
Vegetable Fat (gm)	7.1 (22.1)	7.5 (19.5)	0.90
Saturated Fat (gm)	7.8 (17.4)	3.9 (14.4)	0.17
Monounsaturated Fat (gm)	8.8 (18.2)	5.4 (14.7)	0.25
Carbohydrates (gm)	39.2 (148.7)	21.2 (112.9)	0.43
Dietary Fiber (gm)	1.1 (11.8)	0.5 (11.0)	0.75
Carbohydrates (gm)/Fat (gm)	-1.0 (2.8)	-0.6 (1.7)	0.29
Protein (gm)	21.6 (49.1)	13.1 (38.9)	0.27
Caffeine (mg)	-3.1 (32.6, 157.6)	7.2 (23.9, 189.8)	0.18*
Saccharin (mg)	0.1 (17.5, 24.8)	2.2 (18.9, 53.7)	0.03*
Alcohol (gm)	-0.1 (1.3, 3.2)	0.1 (1.7, 3.8)	0.40*
Cigarette years	0.0002 (0.008, 0.03) [92]	0.001 (0.01, 0.03) [53]	0.37*

N=92/53 for Aggregating/Non-Aggregating Cigarette years
*Wilcoxon Rank Sum Test
**For Chi-Squared Tests, data presented as Median (25th Quartile, 75th Quartile)

TABLE 10

Mean Intrapair Physical Activity Differences of Aggregating and Non-Aggregating Severely Obese and Normal Weight Sibs

Physical Activity	Aggregating Mean (SD)**	Non-Aggregating Mean (SD)**	p-value
Caltrac			
N	83	50	
Total Calories Used	269 (766)	374 (623)	0.39
Total Activity Calories	16 (541)	88 (519)	0.45
Total Calories Used/Body Weight (kg)	-7.8 (9.3)	-6.6 (6.8)	0.40
Total Activity Calories/Body Weight (kg)	-2.8 (6.2)	-2.5 (5.9)	0.78
Questionnaire			
N	92	53	
Blocks/day	-4.9 (-5.3, 9.9)	-1.0 (-1.4, 14.2)	0.11*
Usual Pace of Walking (1=strolling; 2=normal)	-1.0 (0.2, 2.0)	-1.0 (1.0, 2.2)	0.33*
Flights/day	-2.5 (-2.2, 7.4)	-2.6 (0.9, 7.4)	0.37*
Number Times Exercise/week	-0.7 (-0.9, 1.7)	-0.8 (-1.1, 2.9)	0.95*
Exertion Level in Exercise (2=weak; 3=moderate)	-1.2 (0.2, 3.8)	-0.8 (0.6, 4.5)	0.37*
View of Physical Activity	0.01 (1.8, 2.8)	0.01 (1.8, 2.8)	0.71*
Hours of Sleep/weekday	0.02 (6.6, 9.1)	-0.02 (6.4, 8.6)	0.15*
Hours of Sleep/weekend	0.2 (-0.9, 2.0)	0.2 (7.0, 9.7)	0.43*
Hours of Sitting/weekday	1.7 (4.3, 9.1)	0.8 (2.0, 8.8)	0.32*
Hours of Sitting/weekend	1.2 (4.5, 8.9)	1.6 (4.4, 9.3)	0.65*
Hours of Light Activity/weekday	0.08 (2.5, 8.9)	0 (4.1, 10.1)	0.41*
Hours of Light Activity/weekend	0.1 (2.6, 6.9)	0.002 (1.9, 6.9)	0.72*
Hours of Moderate Activity/weekday	-0.4 (0.6, 5.8)	-0.4 (0.4, 6.7)	0.96*
Hours of Moderate Activity/weekend	-0.6 (1.0, 5.5)	-0.04 (1.8, 5.9)	0.59*
Hours of Vigorous Activity/weekday	-0.4 (-0.3, 1.1)	-0.6 (-0.1, 1.0)	0.49*
Hours of Vigorous Activity/weekend	-0.3 (-0.2, 1.7)	-0.9 (-0.7, 1.2)	0.08*

*Wilcoxon Rank Sum Test

**For Chi-Squared Tests, data presented as Median (25th Quartile, 75th Quartile)

TABLE 11

Mean Intrapair SF-36 Differences of Aggregating and Non-Aggregating Severely Obese and Normal Weight Sibs

SF-36: Physiological and Emotional Well-Being	Aggregating Mean (SD) [n=]	Non-Aggregating Mean (SD)[n=]	p-value
General Health	42.7 (23.8) [89]	46.2 (22.6) [50]	0.40
Physical Pain	56.5 (25.9) [89]	58.5 (27.3) [51]	0.67
Emotional Functioning	64.8 (53.4) [92]	60.6 (51.6) [53]	0.64
Physical Functioning	49.3 (27.5) [92]	50.8 (29.1) [53]	0.76
Role Physical	43.9 (40.1) [92]	48.8 (51.7) [53]	0.55
Social	68.0 (34.1) [90]	68.5 (27.6) [51]	0.92
Vitality	32.5 (25.4) [90]	33.1 (24.4) [51]	0.90
Mental	66.3 (24.9) [89]	64.7 (23.8) [51]	0.71

SF-36 Scale Score:
0 = lowest possible score (poor health)
100 = highest possible score (good health)

NOTES TO CHAPTER 5

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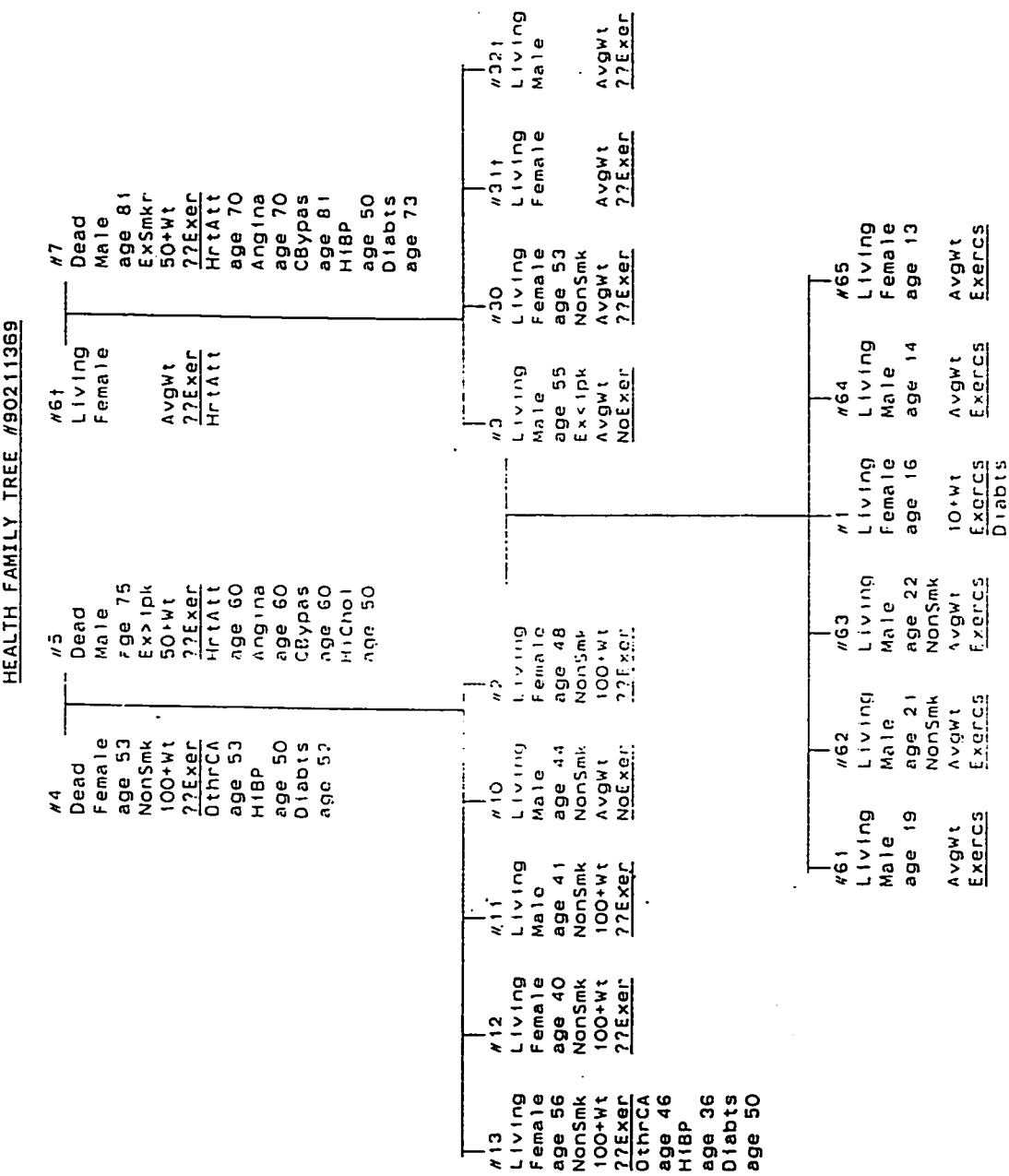
APPENDIX 1

Health Family Tree



APPENDIX 2

Introductory Letters

THE UNIVERSITY OF UTAH

October 3, 1997

Cardiovascular Genetics Research Clinic
Department of Internal Medicine

MARIA LYNN DAINES
1493 SOUTH 500 EAST
KAYSVILLE UT 84037

Dear Mrs Daines:

As part of a high school class, one of your children completed a "Health Family Tree." On the health tree form a consent was given for our department to contact you at a future date regarding research that may pertain to your family. Our department is now conducting a research study that may be of interest to your family, and this letter describes briefly the nature of this study.

In connection with a National Institutes of Health grant, we have received funding to study genetic and environmental factors that determine weight and weight gain. We are especially interested in families where at least one member of the family is overweight to a significant degree. This type of family is ideal to study the genetic and environmental determinations of being overweight.

To verify the "Health Family Tree" record and to briefly explain the research study, we would like to contact you by phone. For your information, participation in the study would include a short visit to our clinic. This visit would include:

Signing a consent form
Filling out diet, physical activity and health questionnaires
Having a fasting blood sample drawn and bringing a urine sample to clinic
Several brief body measurements and blood pressures
Wearing an activity monitor to determine your daily energy expenditure

There is no cost to you for your visit to our clinic, and you will be provided with the results from the standard blood tests. These results include your total cholesterol, triglyceride levels, LDL and HDL cholesterol levels. We will send you a complete analysis of your nutrient intake. This nutrient analysis includes total calories, calories and percent of calories from carbohydrates, fat and protein, as well as the vitamin and mineral content of your diet. A computer analysis of your percent body fat will be included with your results. Lastly, you will discover the number of calories your body uses during the day by wearing a small, "pager-sized" activity monitor. We are providing these results to you, which would normally cost from $200 to $300, as partial compensation for your sacrifice of time to attend our clinic. Also, upon the return of the activity monitor, we will send you $10.

We will be calling you shortly to discuss any questions you might have concerning the research project and to inquire about your interest in participating. We greatly appreciate your support.

Sincerely,

Ted D. Adams, Ph.D. and Maria M. Daines, M.S.
Principal Investigators, Cardiovascular Genetics Research

900 - 196
MOS 29/5-94 uucvg

THE UNIVERSITY OF UTAH

October 3, 1997

Cardiovascular Genetics Research Clinic
Department of Internal Medicine

MARIA LYNN DAINES
1493 SOUTH 500 EAST
KAYSVILLE UT 84037

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In connection with a National Institutes of Health grant, we have received funding to continue our research on genetic and environmental factors that determine weight and weight gain. We are especially interested in families where at least one member of the family is overweight to a significant degree. This type of family is ideal to study the genetic and environmental determinations of being overweight.

To verify the "Family Health Tree" record and to briefly explain the research study, we would like to contact you by phone. Your time commitment will be minimal. The research can all be done by mail and would include:

1. Signing a consent form
2. Filling out diet, physical activity and health questionnaires
3. Wearing an activity monitor to determine your daily energy expenditure

For your participation, we will send you a complete analysis of your nutrient intake. This nutrient analysis includes total calories, calories and percent of calories from carbohydrates, fat and protein, as well as the vitamin and mineral content of your diet. In addition, you will receive the results of a standard health survey which evaluates your physical health and stress level. Lastly, you will discover the number of calories your body uses during the day by wearing an activity monitor. We are providing these results to you, which would normally cost about $100, as partial compensation for your sacrifice of time. Furthermore, upon the return of the activity monitor, we will send you $10.

We will be calling you shortly to discuss any questions you might have concerning the research project and to inquire about your interest in participating. We greatly appreciate your support.

Sincerely,

Ted D. Adams, Ph.D. and Maria M. Daines, M.S.
Principal Investigators, Cardiovascular Genetics Clinic

900 - 196
MOS 30/5-94 uucvg

Cardiovascular Genetics Research Clinic
Room 167
410 Chipeta Way, Research Park
Salt Lake City, Utah 84108
(801) 581-3888 Office

THE UNIVERSITY OF UTAH

October 3, 1997

Cardiovascular Genetics Research Clinic
Department of Internal Medicine

MARIA LYNN DAINES
1493 SOUTH 500 EAST
KAYSVILLE UT 84037

Mrs Daines:

A relative of yours is now participating in a research study by our Cardiovascular Genetics Research Clinic. This relative has given us only your name, address, and telephone number so we could contact you to determine whether or not you would be interested in consenting to participate in this research project. For your information we have described briefly the nature of this study.

In connection with a National Institutes of Health grant, we have received funding to continue our research on genetic and environmental factors that determine weight and weight gain. We are especially interested in families where at least one member of the family is overweight to a significant degree. This type of family is ideal to study the genetic and environmental determinations of being overweight.

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We will be phoning you in the very near future to discuss any questions you might have about this study and to determine whether or not you wish to participate. Thank you for your time and consideration.

Sincerely,

Ted D. Adams, Ph.D. and Maria M. Daines, M.S.
Principal Investigators, Cardiovascular Genetics Clinic

900 - 196
MOS 33/5-94 uucvg

Cardiovascular Genetics Research Clinic
Room 167
410 Chipeta Way, Research Park
Salt Lake City, Utah 84108
(801) 581-3888 Office

THE UNIVERSITY OF UTAH

Cardiovascular Genetics Research Clinic
Department of Internal Medicine

October 3, 1997

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KAYSVILLE UT 84037

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Sincerely,

Ted D. Adams, Ph.D. and Maria M. Daines, M.S.
Principal Investigators, Cardiovascular Genetics Research

900 - 196
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Cardiovascular Genetics Research Clinic
Room 167
410 Chipeta Way, Research Park
Salt Lake City, Utah 84108
(801) 581-3888 Office

THE UNIVERSITY OF UTAH

October 1, 1997

Cardiovascular Genetics Research Clinic
Department of Internal Medicine

MARIA LYNN DAINES
1493 SOUTH 500 EAST
KAYSVILLE UT 84037

Dear Mrs Daines:

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Sincerely,

Ted D. Adams, Ph.D. and Maria M. Daines, M.S.
Principal Investigators, Cardiovascular Genetics Research

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MOS 29/5-94 uucvg

Cardiovascular Genetics Research Clinic
Room 167
410 Chipeta Way, Research Park
Salt Lake City, Utah 84108
(801) 581-3888 Office

APPENDIX 3

Consent Form

CONSENT FOR PARTICIPATION IN AN INVESTIGATIONAL STUDY

The Influences of Environment on Morbid Obesity

INFORMATION

Purpose

The purpose of this study is to determine the influence of the environment on the development of morbid obesity and to assess how the environment affects obesity within families where certain members have been identified as being morbidly obese. The goal of this research is to ultimately contribute to the early detection, control, or prevention of obesity.

Procedure

You will be asked to participate in all or some of the following procedures:

1. Questionnaires about your diet and your family's health status will be collected.
2. You will be asked to wear a small device that determines the amount of daily activity. There are no risks to wearing this devise.
3. Total time to complete the questionnaires will be approximately 45 minutes.

Benefits

The information collected from you and other participants will be analyzed to improve the understanding of heredity and environmental factors leading to morbid obesity. Results of the dietary history, health survey and activity monitor will be given to you.

Confidentiality

All records and information gathered will be held in confidence by the investigator, the sponsor of the research and the Institutional Review Board. They may be inspected by the Food and Drug Administration. Any release of the information derived from these records to scientific organizations, medical journals, etc. will be done only without identification of the participants.

At any time during participation in the investigation, the staff will be willing to answer questions. For questions concerning the research and your rights as a subject, please contact one of the investigators below:

Ted D. Adams, Ph.D.
Fitness Institute, Cardiology
L.D.S. Hospital
(801)321-1396

Maria Daines
Cardiovascular Genetics, Dept. of Medicine
University of Utah
(801)581-3806

If you have any questions regarding your rights as a research subject, or if problems arise which you do not feel you can discuss with the Investigators, please contact Kendell Nelson, Assistant to the Administrator, 801-321-1968.

CONSENT

I understand participation in this study is voluntary and my refusal to participate will involve no penalty or loss of benefits to which I would otherwise be entitled. I may discontinue participation at any time without penalty or loss of benefits to which I should otherwise be entitled.

I understand my participation in this study may be terminated by the investigators without regard to my consent. I understand that if I decide to withdraw from this study, arrangements will be made for an orderly termination and I will be informed of any consequences which may occur upon my decision to withdraw. I understand new findings which develop during the course of the research which may relate to my willingness to continue participation will be provided to me.

I understand the particular treatments or procedure described previously may involve risks to me which are currently unforeseeable.

Records will be held in confidence by the investigators, the sponsor of the research and the Institutional Review Board. They may be inspected by the Food and Drug Administration. Any release of information derived from these records to scientific organizations, medical journals, etc. will be done only without identification of the subjects.

I have read the foregoing and my questions have been answered. I desire to participate in this study and accept the benefits and risks. I have permission for information gathered in this study to be released to Ted D. Adams, Maria Daines and L.D.S. Hospital. A copy of this consent form has been given to me.

Signature of Subject	Date
Parent or Guardian's Signature	Relationship to Subject
Witness	Date

*Signature of parent or guardian is required for subjects age 12 to 17 or those unable to consent.

APPENDIX 4

Individual Questionnaire

Cardiovascular Genetics Research Clinic
Department of Internal Medicine
University of Utah

410 Chipeta Way, Room 161
Salt Lake City, UT 84108
Phone (801)581-3888

INDIVIDUAL QUESTIONNAIRE

1. NAME: _____
(Please print) (Last) (First) (Middle) (Maiden)

2. TODAY'S DATE: _____ (day) _____ (month) _____ (year)

3. DATE OF BIRTH: _____ (day) _____ (month) _____ (year)

4. PHONE NUMBER: _____ - _____ - _____
(area code)

5. SOCIAL SECURITY NUMBER: _____ - ___ - _____

DIRECTIONS: Please circle the correct choice or fill in the blank.

6. SEX:
1) Male
2) Female

7. MARITAL STATUS:
1) Married
2) Single
3) Widowed
4) Divorced
5) Separated

8. RACE:
1) White
2) Black
3) Asian
4) American Indian
5) Hispanic
6) Other

9. RELIGIOUS PREFERENCE (Optional):
A. 1) Catholic
2) Jewish
3) LDS (Mormon)
4) Protestant
5) Other
6) None
B. Do you attend church 2 or more times a month?
1) No
2) Yes

10. INCOME:
What is your total or combined family income, before taxes?
1) less than $5,000
2) $5,000 - 7,499
3) $7,500 - 9,999
4) $10,000 - 14,999
5) $15,000 - 19,999
6) $20,000 - 24,999
7) $25,000 - 34,999
8) $35,000 - 49,999
9) $50,000 or more
10) Retired

11. EDUCATION:
Total Years _____
(12 = high school graduate;
16 = college graduate;
include technical schools)

12. CHILDREN:
Total number including adopted _____

13. HEIGHT & WEIGHT:
1) Height: _____ inches
2) Weight now: _____ lbs.
3) Weight at 20-24 yrs. _____ lbs.
4) What has been your highest weight ever? _____ lbs.
(If female, list highest non-pregnant weight)
5) How old were you at that time? _____

14. ALCOHOL CONSUMPTION:
Do you drink alcoholic beverages (beer, wine, or liquors)?
Please circle one that applies:
1) No
2) Less than once a month
3) Once a month or more with an average of:
_____ 12-16 oz. cans of beer per week
_____ 4-6 oz. glasses of wine per week
_____ shots, jiggers or mixed drinks per week

15. CIGARETTE SMOKING:
A. Please circle one that applies:
1) **Smoker**: Have smoked daily for 1 year or more
2) **Ex-smoker**: Have not smoked for at least one year after having smoked daily for at least one year
3) **Non-smoker**: Have never smoked daily for at least one year
B. If **smoker** or **ex-smoker**, circle **average** amount and indicate number of years smoked. Choose one only.
1) Less than 1 pack a day for _____ years.
2) About 1 pack a day for _____ years.
3) One-two packs a day for _____ years.
4) Two or more packs a day for _____ years.
C. List the last year in which you smoked. _____

16. **DIABETES:**
    A. Have you ever been told by a doctor that you suffer from diabetes?
        1) Yes
        2) No
    B. If Yes, circle any of the following that apply.
        1) Insulin injections have been prescribed by my doctor for control of my blood sugar
        2) Medication (pills or tablets) have been prescribed for control of my blood sugar
        3) I monitor my urine and/or blood sugar at home as directed by my doctor
        4) A special diet for control of my blood sugar has been prescribed by my doctor

17. **ADULT HEIGHT:**
    At what age did you reach your approximate adult height?
        1) 10-11 yrs. (5th grade)
        2) 11-12 yrs. (6th grade)
        3) 12-13 yrs. (7th grade)
        4) 13-14 yrs. (8th grade)
        5) 14-15 yrs. (9th grade)
        6) 15-16 yrs. (10th grade)
        7) 16-17 yrs. (11th grade)
        8) 17 + yrs.

18. **PERSONAL BIRTH HISTORY:**
    A. Was your birth (delivery):
        1) Normal (no complications)
        2) C-section
        3) Emergency C-section
        4) Breech
        5) Prolonged delivery
        6) I don't know
    B. Was there a period of time during your delivery when you as the baby did not receive enough oxygen?
        1) Yes
        2) No
        3) I don't know

19. **HEAD TRAUMA:**
    A. Have you ever sustained a head injury?
        1) Yes
        2) No
    B. Were you unconscious for a period of 10 minutes?
        1) Yes
        2) No
    C. Describe: _____
    _____

20. **EMOTIONAL HEALTH:**
    A. Are any members of your family (parents or siblings) depressed or struggle with depression?
        1) Yes
        2) No
        3) I don't know
    B. If yes, how many? _____
    C. Of the depressed members:
        1) How many are thin? _____
        2) How many are normal weight? _____
        3) How many are overweight? _____
        4) How many are obese? _____

FEMALES AGE 10 AND OLDER

21. At what age did you begin menstruation (having periods)? If you have not started menstruating, please skip. _____ yrs. old

22. When did your last menstrual period begin?

    _____ _____ _____
    day month year

23 Do you now or have you ever taken birth control pills?
    1) No
    2) Yes

24. If yes what is the longest single period of time you have taken birth control pills?
    1) Less than 1 year
    2) More than 1 year (_____ _____)
    years months

25. Are you presently taking birth control pills?
    1) No
    2) Yes for (_____ _____)
    years months

26. Besides birth control pills, are you taking any hormone (estrogen and/or progesterone) replacement therapy?
    1) No
    2) Yes (List)_____

27. Have you ever been pregnant?
    1) No
    2) Yes , number of times _____

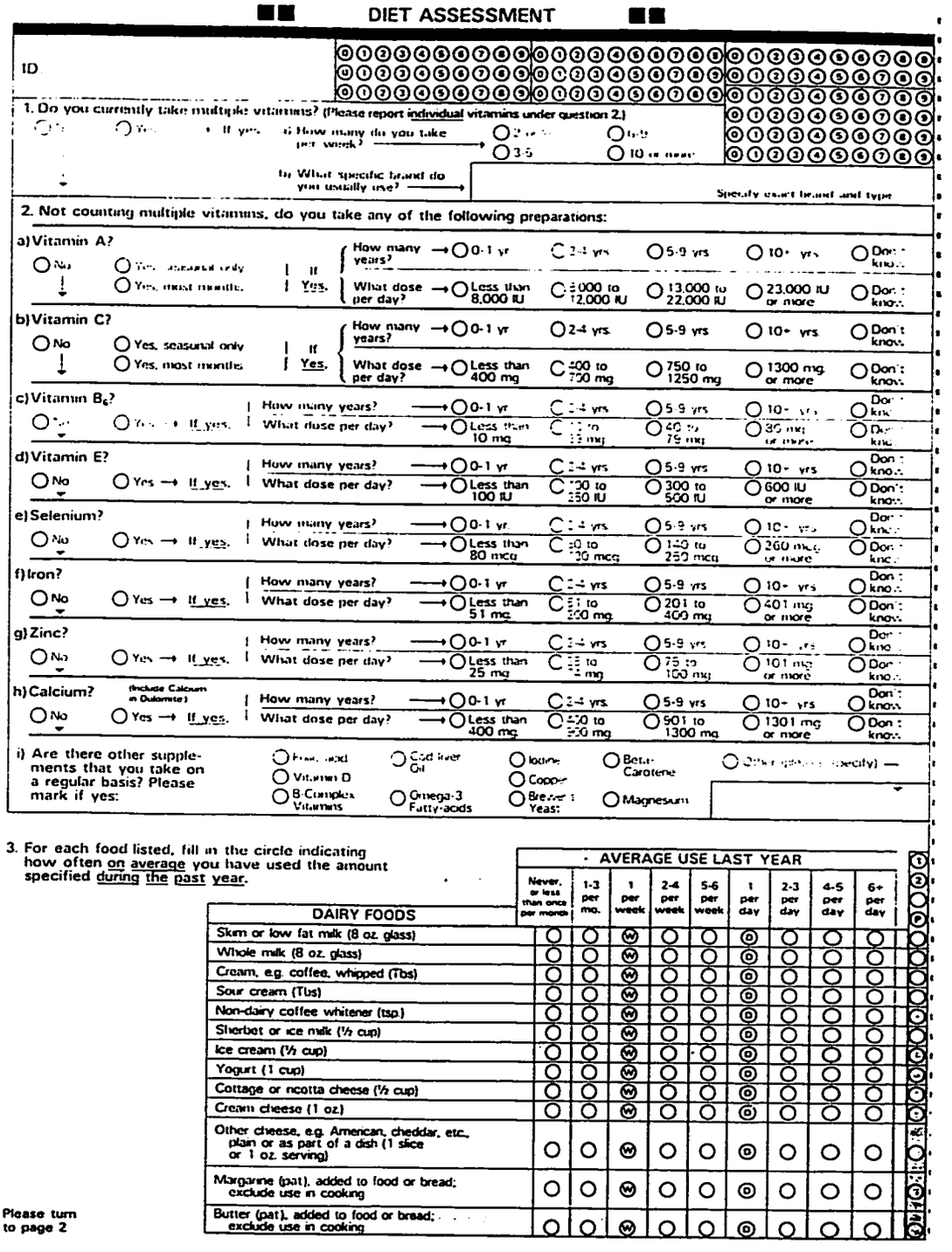
28. Are you now pregnant?
    1) No
    2) Yes - Estimated date of delivery

    _____ _____ _____
    day month year
    3) Possibly but not confirmed by blood test

29. Which of the following best describes you?
    (Please circle only one)
    1) I have not yet started menopause.
    2) I am presently going through menopause.
    3) I have already gone through menopause and have not had any periods for _____ years.
    4) I have had a hysterectomy (removal or uterus only) at age _____ and have not had any hot flashes.
    5) I have had a hysterectomy (removal of uterus only) at age _____ and began having hot flashes at age _____.
    6) I have had a hysterectomy and oophorectomy (removal of uterus and one or more ovaries) at age _____.
    7) Other (Explain) _____
    _____

APPENDIX 5

Semiquantitative Food Frequency Questionnaire



DIET ASSESSMENT

ID

1. Do you currently take multiple vitamins? (Please report individual vitamins under question 2.)
○ No ○ Yes → If yes: a) How many do you take per week? ○ 2 or less ○ 3-6 ○ 7-9 ○ 10 or more
b) What specific brand do you usually use? → Specify exact brand and type

2. Not counting multiple vitamins, do you take any of the following preparations:

a) Vitamin A?
○ No ○ Yes, seasonal only ○ Yes, most months | If Yes, How many years? → ○ 0-1 yr ○ 2-4 yrs ○ 5-9 yrs ○ 10+ yrs ○ Don't know
What dose per day? → ○ Less than 8,000 IU ○ 8,000 to 12,000 IU ○ 13,000 to 22,000 IU ○ 23,000 IU or more ○ Don't know

b) Vitamin C?
○ No ○ Yes, seasonal only ○ Yes, most months | If Yes, How many years? → ○ 0-1 yr ○ 2-4 yrs ○ 5-9 yrs ○ 10+ yrs ○ Don't know
What dose per day? → ○ Less than 400 mg ○ 400 to 750 mg ○ 750 to 1250 mg ○ 1300 mg or more ○ Don't know

c) Vitamin B_6?
○ No ○ Yes → If yes, How many years? → ○ 0-1 yr ○ 2-4 yrs ○ 5-9 yrs ○ 10+ yrs ○ Don't know
What dose per day? → ○ Less than 10 mg ○ 10 to 39 mg ○ 40 to 79 mg ○ 80 mg or more ○ Don't know

d) Vitamin E?
○ No ○ Yes → If yes, How many years? → ○ 0-1 yr ○ 2-4 yrs ○ 5-9 yrs ○ 10+ yrs ○ Don't know
What dose per day? → ○ Less than 100 IU ○ 100 to 250 IU ○ 300 to 500 IU ○ 600 IU or more ○ Don't know

e) Selenium?
○ No ○ Yes → If yes, How many years? → ○ 0-1 yr ○ 2-4 yrs ○ 5-9 yrs ○ 10+ yrs ○ Don't know
What dose per day? → ○ Less than 80 mcg ○ 80 to 130 mcg ○ 140 to 250 mcg ○ 260 mcg or more ○ Don't know

f) Iron?
○ No ○ Yes → If yes, How many years? → ○ 0-1 yr ○ 2-4 yrs ○ 5-9 yrs ○ 10+ yrs ○ Don't know
What dose per day? → ○ Less than 51 mg ○ 51 to 200 mg ○ 201 to 400 mg ○ 401 mg or more ○ Don't know

g) Zinc?
○ No ○ Yes → If yes, How many years? → ○ 0-1 yr ○ 2-4 yrs ○ 5-9 yrs ○ 10+ yrs ○ Don't know
What dose per day? → ○ Less than 25 mg ○ 25 to 74 mg ○ 75 to 100 mg ○ 101 mg or more ○ Don't know

h) Calcium? (Include Calcium in Dolomite)
○ No ○ Yes → If yes, How many years? → ○ 0-1 yr ○ 2-4 yrs ○ 5-9 yrs ○ 10+ yrs ○ Don't know
What dose per day? → ○ Less than 400 mg ○ 400 to 900 mg ○ 901 to 1300 mg ○ 1301 mg or more ○ Don't know

i) Are there other supplements that you take on a regular basis? Please mark if yes:
○ Iron, iron acid ○ Cod liver Oil ○ Iodine ○ Beta-Carotene ○ Other (please specify) →
○ Vitamin D ○ Copper
○ B-Complex Vitamins ○ Omega-3 Fatty-acids ○ Brewer's Yeast ○ Magnesium

3. For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year.

DAIRY FOODS	AVERAGE USE LAST YEAR: Never, or less than once per month	1-3 per mo.	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
Skim or low fat milk (8 oz. glass)	○	○	ⓦ	○	○	ⓓ	○	○	○
Whole milk (8 oz. glass)	○	○	ⓦ	○	○	ⓓ	○	○	○
Cream, e.g. coffee, whipped (Tbs)	○	○	ⓦ	○	○	ⓓ	○	○	○
Sour cream (Tbs)	○	○	ⓦ	○	○	ⓓ	○	○	○
Non-dairy coffee whitener (tsp.)	○	○	ⓦ	○	○	ⓓ	○	○	○
Sherbet or ice milk (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Ice cream (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Yogurt (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Cottage or ricotta cheese (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Cream cheese (1 oz.)	○	○	ⓦ	○	○	ⓓ	○	○	○
Other cheese, e.g. American, cheddar, etc., plain or as part of a dish (1 slice or 1 oz. serving)	○	○	ⓦ	○	○	ⓓ	○	○	○
Margarine (pat), added to food or bread; exclude use in cooking	○	○	ⓦ	○	○	ⓓ	○	○	○
Butter (pat), added to food or bread; exclude use in cooking	○	○	ⓦ	○	○	ⓓ	○	○	○

Please turn to page 2

3. (Continued) Please fill in your average use, during the past year, of each specified food.

Please try to average your seasonal use of foods over the entire year. For example, if a food such as cantaloupe is eaten 4 times a week during the approximate 3 months that it is in season, then the average use would be once per week.

FRUITS	Never, or less than once per month	1-3 per mo.	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
Raisins (1 oz or small pack) or grapes	○	○	ⓦ	○	○	ⓓ	○	○	○
Prunes (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Bananas (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Cantaloupe (½ melon)	○	○	ⓦ	○	○	ⓓ	○	○	○
Watermelon (1 slice)	○	○	ⓦ	○	○	ⓓ	○	○	○
Fresh apples or pears (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Apple juice or cider (small glass)	○	○	ⓦ	○	○	ⓓ	○	○	○
Oranges (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Orange juice (small glass)	○	○	ⓦ	○	○	ⓓ	○	○	○
Grapefruit (½)	○	○	ⓦ	○	○	ⓓ	○	○	○
Grapefruit juice (small glass)	○	○	ⓦ	○	○	ⓓ	○	○	○
Other fruit juices (small glass)	○	○	ⓦ	○	○	ⓓ	○	○	○
Strawberries, fresh, frozen or canned (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Blueberries, fresh, frozen or canned (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Peaches, apricots or plums (1 fresh, or ½ cup canned)	○	○	ⓦ	○	○	ⓓ	○	○	○

VEGETABLES	Never, or less than once per month	1-3 per mo.	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
Tomatoes (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Tomato juice (small glass)	○	○	ⓦ	○	○	ⓓ	○	○	○
Tomato sauce (½ cup) e.g. spaghetti sauce	○	○	ⓦ	○	○	ⓓ	○	○	○
Red chili sauce (1 Tbs)	○	○	ⓦ	○	○	ⓓ	○	○	○
Tofu or soybeans (3-4 oz)	○	○	ⓦ	○	○	ⓓ	○	○	○
String beans (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Broccoli (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Cabbage or cole slaw (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Cauliflower (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Brussels sprouts (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Carrots, raw (½ carrot or 2-4 sticks)	○	○	ⓦ	○	○	ⓓ	○	○	○
Carrots, cooked (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Corn (1 ear or ½ cup frozen or canned)	○	○	ⓦ	○	○	ⓓ	○	○	○
Peas, or lima beans (½ cup fresh, frozen, canned)	○	○	ⓦ	○	○	ⓓ	○	○	○
Mixed vegetables (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Beans or lentils, baked or dried (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Yellow (winter) squash (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Eggplant, zucchini, or other summer squash (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Yams or sweet potatoes (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Spinach, cooked (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Spinach, raw as in salad	○	○	ⓦ	○	○	ⓓ	○	○	○
Kale, mustard or chard greens (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Iceberg or head lettuce (serving)	○	○	ⓦ	○	○	ⓓ	○	○	○
Romaine or leaf lettuce (serving)	○	○	ⓦ	○	○	ⓓ	○	○	○
Celery (4" stick)	○	○	ⓦ	○	○	ⓓ	○	○	○
Beets (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Alfalfa sprouts (½ cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Garlic, fresh or powdered (1 clove or shake)	○	○	ⓦ	○	○	ⓓ	○	○	○

EGGS, MEAT, ETC.	Never, or less than once per month	1-3 per mo.	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
Eggs (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Chicken or turkey, with skin (4-6 oz)	○	○	ⓦ	○	○	ⓓ	○	○	○
Chicken or turkey, without skin (4-6 oz)	○	○	ⓦ	○	○	ⓓ	○	○	○
Bacon (2 slices)	○	○	ⓦ	○	○	ⓓ	○	○	○
Hot dogs (1)	○	○	ⓦ	○	○	ⓓ	○	○	○

Please go to page 3

3. (Continued) Please fill in your average use, during the past year, of each specified food.

MEATS (CONTINUED)	Never, or less than once per month	1-3 per mo.	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
Processed meats, e.g. sausage, salami, bologna, etc. (pieces or slices)	○	○	ⓦ	○	○	ⓓ	○	○	○
Liverwurst	○	○	ⓦ	○	○	ⓓ	○	○	○
Hamburger (1 patty)	○	○	ⓦ	○	○	ⓓ	○	○	○
Beef, pork, or lamb as a sandwich or mixed dish, e.g. stew, casserole, lasagne, etc	○	○	ⓦ	○	○	ⓓ	○	○	○
Beef, pork, or lamb as a main dish, e.g. steak, roast, ham, etc. (4-6 oz)	○	○	ⓦ	○	○	ⓓ	○	○	○
Canned tuna fish (3-4 oz)	○	○	ⓦ	○	○	ⓓ	○	○	○
Dark meat fish, e.g. mackerel, salmon, sardines, bluefish, swordfish (3-5 oz)	○	○	ⓦ	○	○	ⓓ	○	○	○
Other fish (3-5 oz)	○	○	ⓦ	○	○	ⓓ	○	○	○
Shrimp, lobster, scallops as a main dish	○	○	ⓦ	○	○	ⓓ	○	○	○

BREADS, CEREALS, STARCHES	Never, or less than once per month	1-3 per mo	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
Cold breakfast cereal (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Cooked oatmeal (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Other cooked breakfast cereal (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
White bread (slice), excluding pita bread	○	○	ⓦ	○	○	ⓓ	○	○	○
Dark bread (slice)	○	○	ⓦ	○	○	ⓓ	○	○	○
English muffins, bagels, or rolls (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Muffins or biscuits (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Brown rice (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
White rice (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Pasta, e.g. spaghetti, noodles, etc. (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Other grains, e.g. bulgar, kasha, couscous, etc. (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Pancakes or waffles (serving)	○	○	ⓦ	○	○	ⓓ	○	○	○
French fried potatoes (4 oz)	○	○	ⓦ	○	○	ⓓ	○	○	○
Potatoes, baked, boiled (1) or mashed (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Potato chips or corn chips (small bag or 1 oz)	○	○	ⓦ	○	○	ⓓ	○	○	○
Crackers, Triskets, Wheat Thins (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Pizza (2 slices)	○	○	ⓦ	○	○	ⓓ	○	○	○

		BEVERAGES	Never, or less than once per month	1-3 per mo.	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
CARBONATED BEVERAGES	Low Calorie (sugar-free) types	Low calorie cola, e.g. Tab with caffeine	○	○	ⓦ	○	○	ⓓ	○	○	○
		Low calorie caffeine-free cola, e.g. Pepsi Free	○	○	ⓦ	○	○	ⓓ	○	○	○
Consider the serving size as 1 glass, bottle or can for these carbonated beverages.		Other low calorie carbonated beverage, e.g. Fresca, Diet 7-Up, diet ginger ale	○	○	ⓦ	○	○	ⓓ	○	○	○
	Regular types (not sugar-free)	Coke, Pepsi, or other cola with sugar	○	○	ⓦ	○	○	ⓓ	○	○	○
		Caffeine Free Coke, Pepsi, or other cola with sugar	○	○	ⓦ	○	○	ⓓ	○	○	○
		Other carbonated beverage with sugar, e.g. 7-Up, ginger ale	○	○	ⓦ	○	○	ⓓ	○	○	○
OTHER BEVERAGES		Hawaiian Punch, lemonade, or other non-carbonated fruit drinks (1 glass, bottle, can)	○	○	ⓦ	○	○	ⓓ	○	○	○
		Decaffeinated coffee (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
		Coffee (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
		Tea (1 cup), not herbal teas	○	○	ⓦ	○	○	ⓓ	○	○	○
		Beer (1 glass, bottle, can)	○	○	ⓦ	○	○	ⓓ	○	○	○
		Red wine (4 oz. glass)	○	○	ⓦ	○	○	ⓓ	○	○	○
		White wine (4 oz. glass)	○	○	ⓦ	○	○	ⓓ	○	○	○
		Liquor, e.g. whiskey, gin, etc. (1 drink or shot)	○	○	ⓦ	○	○	ⓓ	○	○	○

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ID:

3. (Continued) Please fill in your average use during the past year of each specified food.

SWEETS, BAKED GOODS, MISCELLANEOUS	Never or less than once per month	1-3 per mo	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day
Chocolate (bars or pieces) eg. Hershey's, M&M's	○	○	ⓦ	○	○	ⓓ	○	○	○
Candy bars, eg. Snickers, Milky Way, Reese's	○	○	ⓢ	○	○	ⓓ	○	○	○
Candy without chocolate (1 oz)	○	○	ⓦ	○	○	ⓓ	○	○	○
Cookies, home baked (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Cookies, ready made (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Brownies (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Doughnuts (1)	○	○	ⓦ	○	○	ⓓ	○	○	○
Cake, home baked (slice)	○	○	ⓦ	○	○	ⓓ	○	○	○
Cake, ready made (slice)	○	○	ⓦ	○	○	ⓓ	○	○	○
Sweet roll, coffee cake or other pastry, home baked (serving)	○	○	ⓦ	○	○	ⓓ	○	○	○
Sweet roll, coffee cake or other pastry, ready made (serving)	○	○	ⓦ	○	○	ⓓ	○	○	○
Pie, homemade (slice)	○	○	ⓦ	○	○	ⓓ	○	○	○
Pie, ready made (slice)	○	○	ⓦ	○	○	ⓓ	○	○	○
Jams, jellies, preserves, syrup, or honey (1 Tbs)	○	○	ⓦ	○	○	ⓓ	○	○	○
Peanut butter (Tbs)	○	○	ⓦ	○	○	ⓓ	○	○	○
Popcorn (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Nuts (small packet or 1 oz)	○	○	ⓦ	○	○	ⓓ	○	○	○
Bran, added to food (1 Tbs)	○	○	ⓦ	○	○	ⓓ	○	○	○
Wheat germ (1 Tbs)	○	○	ⓦ	○	○	ⓓ	○	○	○
Chowder or cream soup (1 cup)	○	○	ⓦ	○	○	ⓓ	○	○	○
Oil and vinegar dressing, e.g. Italian (1 Tbs)	○	○	ⓦ	○	○	ⓓ	○	○	○
Mayonnaise or other creamy salad dressing (1 Tbs)	○	○	ⓦ	○	○	ⓓ	○	○	○
Mustard, dry or prepared (1 tsp)	○	○	ⓦ	○	○	ⓓ	○	○	○
Pepper (1 shake)	○	○	ⓦ	○	○	ⓓ	○	○	○
Salt (1 shake)	○	○	ⓦ	○	○	ⓓ	○	○	○

4. How much of the visible fat on your meats do you remove before eating?
○ Remove all visible fat ○ Remove small part of fat
○ Remove majority ○ Remove none
○ (Don't eat meat)

5. What kind of fat do you usually use for frying and sautéing? (Exclude "Pam"-type spray)
○ Real butter ○ Vegetable oil ○ Lard
○ Margarine ○ Vegetable shortening

6. What kind of fat do you usually use for baking?
○ Real butter ○ Vegetable oil ○ Lard
○ Margarine ○ Vegetable shortening

7. What form of margarine do you usually use?
○ None ○ Stick ○ Tub ○ Spread
○ Low-calorie stick ○ Low-calorie tub

8. How often do you eat food that is fried at home? (Exclude the use of "Pam"-type spray)
○ Daily ○ 4-6 times per week
○ 1-3 times per week ○ Less than once a week

9. How often do you eat fried food away from home? (e.g. french fries, fried chicken, fried fish)
○ Daily ○ 4-6 times per week
○ 1-3 times per week ○ Less than once a week

10. How many teaspoons of sugar do you add to your beverages or food each day? ⟶ tsp

11. What type of cooking oil do you usually use? ⟶ Specify type and brand

12. What kind of cold breakfast cereal do you usually use? ⟶ Specify type and brand

13. Are there any other important foods that you usually eat at least once per week?

Include for example: paté, tortillas, yeast, cream sauce, custard, horseradish, parsnips, rhubarb, radishes, fava beans, carrot juice, coconut, avocado, mango, papaya, dried apricots, dates, figs.

(Do not include dry spices and do not list something that has been listed in the previous sections.)

Other foods that you usually use at least once per week	Usual serving size	Servings per week
(a)		
(b)		
(c)		
(d)		

APPENDIX 6

Weight History and Physical Activity Questionnaire

WEIGHT HISTORY AND ACTIVITY QUESTIONNAIRE

We are interested in studying how genetics affects the body weight of a person. Please answer the following questions to the best of your knowledge. All the information will be kept strictly confidential.

1. If you consider yourself obese, at what age in years, would you estimate your obesity occurred?

   ___ 0-10 ___ 11-19 ___ 20-29 ___ 30-39 ___ 40-49 ___ 50 +

2. In addition to the above information, can you specifically remember an age in years when your obesity occurred?

   ___ Yes, my obesity onset was at age ___.
   ___ No, I cannot remember when obesity occurred.
   ___ This question is not applicable to me.

3. Describe your weight between the ages:

	Thin	Average	Somewhat Overweight	Very Overweight
1 - 5 yrs.	___	___	___	___
6 -11 yrs.	___	___	___	___
12-17 yrs.	___	___	___	___
18-29 yrs.	___	___	___	___
30-49 yrs.	___	___	___	___
50 yrs. +	___	___	___	___

4. How many times in your life would you estimate you have lost the number of pounds shown below?

Weight Lost	Number of Times
11-20 pounds	_____
21-30 pounds	_____
31-50 pounds	_____
51 + pounds	_____

5. What do you consider to be your usual weight (weight you have been most of your adult life)? _____

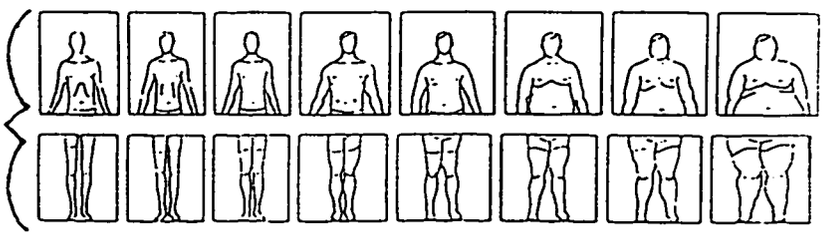
6. When you gain weight, where do you gain? (Check **all** that apply to you.)

   ___ a. waist, abdomen
   ___ b. hips, thighs, buttocks
   ___ c. all over
   ___ d. elsewhere (specify) _____

7. Please look at the figures below to answer the following questions:

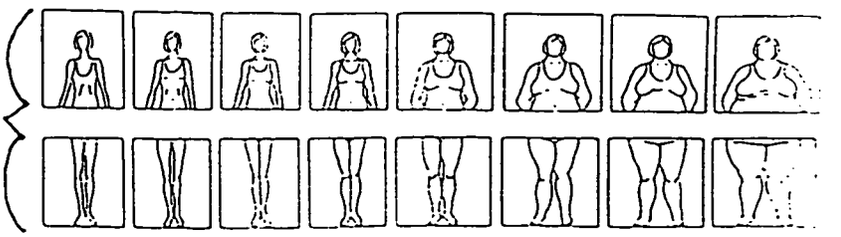
Top	Bottom	
___	___	a. From the figures corresponding with your own sex, choose the top and bottom figure that looks the most like your current figure (or before any medical treatment).
___	___	b. Choose the top and bottom female figure that looks most like your **mother's** figure during her middle adult life.
___	___	c. Choose the top and bottom male figure that looks most like your **father's** figure during his middle adult life.

Male



A B C D E F G H

Female



8. How many city blocks or their equivalent do you regularly walk each **day**?

___ blocks/day (Let 12 blocks = 1 mile)

9. What is your usual pace of walking? (please check one)

___ a. casual or strolling (less than 2 mph)
___ b. average or normal (2 to 3 mph)
___ c. fairly brisk (3 to 4 mph)
___ d. brisk or striding (4 mph or faster)

10. Which of these statements best expresses your view? (please check one)

___ a. I do enough physical activity to keep healthy.
___ b. I ought to do more physical activity.
___ c. Don't know.

11. At least once a **week**, do you engage in regular activity akin to brisk walking, jogging, bicycling, swimming, etc. long enough to work up a sweat, get your heart thumping, or get out of breath?

___ Yes, ___ number of times per week at _____ activity
___ No, reason why _____

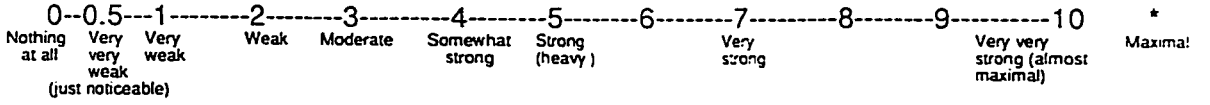
12. List any sports or recreation you have actively participated in during the past year. Please remember seasonal sports or events.

Sport, Recreation, or Other Physical Activity	Number of Times/Year	Average Time/Episode Hours	Minutes	Years Participation
a.				
b.				
c.				
d.				
e.				
f.				
g.				

13. How many flights of stairs do you climb **up** each day?

___ flights/day (Let 1 flight = 10 steps)

14. When you are exercising in your usual fashion, how would you rate your level of exertion (degree of effort)? Please circle **one** number.



15. On a usual weekday and a weekend day, how much time do you spend on the following activities? Total for each day should add to **24 hours**.

Activity	Usual **Weekday** Hours/Day	Usual **Weekend** Hours/Day
a. **Vigorous** activity (digging in garden, strenuous sports, jogging, aerobic dancing, sustained swimming, brisk walking, heavy carpentry, bicycling on hills, etc.)		
b. **Moderate** activity (housework, light sports, regular walking, golf, yard work, lawn mowing, painting, repairing, light carpentry, ballroom dancing, bicycling on level ground, etc.)		
c. **Light** activity (office work, driving a car, strolling, personal care, standing with little motion, etc.)		
d. **Sitting** activity (eating, reading, desk work, watching TV, listening to radio, etc.)		
e. **Sleeping** or reclining		
Total =	24 hours	24 hours

APPENDIX 7

SF-36 Form

HEALTH STATUS QUESTIONNAIRE

INSTRUCTIONS:

This survey asks for your views about your health. This information will be summarized in your medical reco and will help your doctors keep track of how well you are able to do your usual activities. Answer every questi by filling in the correct circle. If you are unsure about how to answer a question, please give the best answer y can and attach a separate piece of paper with your comments (please reference the question number with yo comment).

MARKING INSTRUCTIONS	
-Use a No. 2 pencil ONLY. *-Make dark heavy marks that fill the circle completely.* *-Erase unwanted marks clearly.* *-Make no stray marks on this answer sheet.*	
PROPER MARK ○ ● ○	*IMPROPER MARKS* ⊘ ⊗ ◐

1. In general, would you say your health is: ○ Excellent ○ Very Good ○ Good ○ Fair ○ Poor

2. Compared to one year ago, how would you rate your health in general now?

   ○ Much better now than 1 year ago
   ○ Somewhat better now than 1 year ago
   ○ About the same
   ○ Somewhat worse now than 1 year ago
   ○ Much worse now than 1 year ago

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	○	○	○
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf.	○	○	○
c. Lifting or carrying groceries.	○	○	○
d. Climbing several flights of stairs.	○	○	○
e. Climbing one flight of stairs.	○	○	○
f. Bending, kneeling or stooping.	○	○	○
g. Walking more than one mile.	○	○	○
h. Walking several blocks.	○	○	○
i. Walking one block.	○	○	○
j. Bathing or dressing yourself.	○	○	○

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular dai activities **as a result of your physical health?** (Fill in one circle on each line.)

	Yes	No
a. Cut down the amount of time you spent on work or other activities.	○	○
b. Accomplished less than you would like.	○	○
c. Were limited in the kind of work or other activities.	○	○
d. Had difficulty performing the work or other activities (for example, it took extra effort).	○	○

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular dai activities as a result of any emotional problems (such as feeling depressed or anxious)? (Fill in one circle c each line.)

	Yes	No
a. Cut down the amount of time you spent on work or other activities.	O	O
b. Accomplished less than you would like.	O	O
c. Didn't do work or other activities as carefully as usual.	O	O

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with you normal social activities with family, friends, neighbors or groups? (Fill in one circle.)

O Not at all O Slightly O Moderately O Quite a bit O Extremely

7. How much **bodily pain** have you had during the **past 4 weeks**? (Fill in one circle.)

O None O Very Mild O Mild O Moderate O Severe O Very Severe

8. During the **past 4 weeks**, how much did pain interfere with your normal work (including both work outside th home and housework)? (Fill in one circle.)

O Not at all O Slightly O Moderately O Quite a bit O Extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For eac question, please give the one answer that comes closest to the way you have been feeling. How much of the tim during the **past 4 weeks** . . . (Fill in one circle on each line.)

	All Of the Time	Most Of the Time	A Good Bit of the Time	Some Of the Time	A Little Of the Time	Nor Of t Tim
a. Did you feel full of pep?	O	O	O	O	O	C
b. Have you been a very nervous person?	O	O	O	O	O	C
c. Have you felt so down in the dumps nothing could cheer you up?	O	O	O	O	O	C
d. Have you felt calm and peaceful?	O	O	O	O	O	C
e. Did you have a lot of energy?	O	O	O	O	O	C
f. Have you felt downhearted and blue?	O	O	O	O	O	C
g. Did you feel worn out?	O	O	O	O	O	C
h. Have you been a happy person?	O	O	O	O	O	C
i. Did you feel tired?	O	O	O	O	O	C

10. During the **past 4 weeks**, how much of the time has your physical health or emotional problems interfered wit your social activities (like visiting with friends, relatives, etc.)?

O All of the time O Most of the time O Some of the time O A little of the time . O None of the tin

11. Please choose the answer that best describes how true or false each of the following statements is for you.

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
a. I seem to get sick a little easier than other people.	O	O	O	O	O
b. I am as healthy as anybody I know.	O	O	O	O	O
c. I expect my health to get worse.	O	O	O	O	O
d. My health is excellent.	O	O	O	O	O

APPENDIX 8

Caltrac Form

DAY 1:

NIGHT
CALS USED _____

CALS ACTM _____

Estimated flights of stairs climbed* _____

DAY 2:

MORNING
CALS USED _____

CALS ACTM _____

NIGHT
CALS USED _____

CALS ACTM _____

Estimated flights of stairs climbed* _____

DAY 3:

MORNING
CALS USED _____

CALS ACTM _____

NIGHT
CALS USED _____

CALS ACTM _____

Estimated flights of stairs climbed* _____

---

* 1 Flight = 10 Stairs

CALTRAC INSTRUCTIONS

1. Caltrac is to be worn for three consecutive days.

2. Prior to wearing Caltrac on morning of **Day 1**:
   a. Hold SHIFT and press ENTER key. This clears all calories from the units memory.
   b. If Right Handed, secure Caltrac on Right Hip. If Left Handed, secure Caltrac on Left Hip.

3. Caltrac should read CALS USED while wearing.

4. Each night before going to bed:
   a. Take off Caltrac.
   b. Push DISPLAY until it reads CALS USED. Record number on back of this card.
   c. Then push DISPLAY until it reads CALS USED/ACTM. Record number on back of this card.
   d. Estimate the number of times you climbed a flight of stairs today (1 flight = 10 stairs). Record on back of card.

5. First thing in the morning of **Day 2** and **Day 3**:
   a. Push DISPLAY until it reads CALS USED. Record number on back of this card.
   b. Then push DISPLAY until it reads CALS USED/ACTM. Record number on back of this card.
   b. Place on hip.

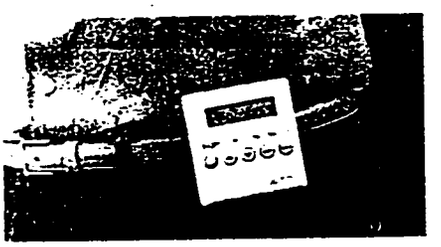
6. Cautions:
   a. Do NOT drop Caltrac on hard surfaces.
   b. Caltrac is NOT waterproof. It is not meant to be used while showering, bathing, swimming or outdoors in the rain or snow without being covered by protective clothing.
   c. If you are involved in strenuous activity where you will perspire, wear Caltrac, but please avoid skin contact. If Caltrac is exposed to water, the unit may be damaged. Therefore, dry it immediately with a dry cloth.
   d. When you use the bathroom or undress, please take the unit off of your clothing, set it aside and then replace it.
   e. If calories are not coming out, batteries are probably low. Call Maria Daines at 581-3888 or 451-7674.

7. When the Caltrac has been worn for three days:
   a. Put Caltrac back in "bubbled" plastic bag.
   b. Place covered Caltrac in the insert inside the box.
   c. Close box and seal with stickers on ends.
   d. If not previously done, put stamps and address label on box.
   e. Mail.

APPENDIX 9

Caltrac

CALTRAC™



Correct Horitontal Position

Muscle Dynamics
FITNESS NETWORK

Correct "Below Navel" Position

APPENDIX 10

Nutrition Report

DIETARY ASSESSMENT FOR ID 72493962 :	YOUR AVERAGE DAILY INTAKE	RECOMMENDED INTAKE					
	AGE	4-6	7-10	11-14	15-18	adult	
TOTAL CALORIES	2234.1 CALS	SEE PAGE 2					
PERCENTAGE OF TOTAL CALORIES FROM:							
PROTEIN	18 %	12-15 %					
FATS	23 %	LESS THAN 30 %					
-SATURATED FATS	9 %	10 % OR LESS					
-POLY UNSATURATED FATS	3 %	10 % OR LESS					
-MONO UNSATURATED FATS	8 %	10 % OR LESS					
CARBOHYDRATES	61 %	55-60 %					
-SUCROSE	11 %	LESS THAN 10 %					
TOTAL PROTEIN	103.6 GM	1.1	1.0	1.0	0.9	0.8	
		1.1	1.0	1.0	0.8	0.8	
TOTAL CARBOHYDRATES	350.5 GM	SEE PAGE 5					
TOTAL FATS	58.7 GM	SEE PAGE 4					
TOTAL CHOLESTEROL	265.4 MG	LESS THAN 300 MG					
DIETARY FIBER	36.5 GM	SEE PAGE 5					
VITAMIN A	33478.3 IU	2500	3300	5000	5000	5000	IU (M)
		2500	3300	4000	4000	4000	IU (F)
VITAMIN C	176.8 MG	45	45	50	60	60	MG
VITAMIN B6	2.9 MG	1.1	1.4	1.7	2.0	2.0	MG (M)
		1.1	1.4	1.4	1.5	1.6	MG (F)
VITAMIN D	434.3 IU	400	400	400	400	200	IU
IRON	21.03 MG	10	10	12	12	10	
		10	10	15	15	15	10(51+)
CALCIUM	1583.8 MG	300	300	1200	1200	800-1200	MG
VITAMIN B1. THIAMIN	2.17 MG	0.9	1.0	1.3	1.5	1.2-1.5	MG (M)
		0.9	1.0	1.1	1.1	1.0-1.1	MG (F)
VITAMIN B2. RIBOFLAVIN	3.05 MG	1.1	1.2	1.5	1.8	1.4-1.7	MG (M)
		1.1	1.2	1.3	1.3	1.2-1.3	MG (F)
NIACIN	25.07 MG	12	13	17	20	15-19	MG (M)
		12	13	15	15	13-15	MG (F)
VITAMIN B12	8.159 MCG	1.0	1.4	2.0	2.0	2.0	MCG
VITAMIN E	6.58 MG	7	7	10	10	10	MG (M)
		7	7	8	8	8	MG (F)

APPENDIX 11

Clinical Characteristics of Morbidly Obese Subjects: A Comparison of Familial and Nonfamilial Pedigrees

Clinical Characteristics of Morbidly Obese Subjects:

A Comparison of Familial and Nonfamilial Pedigrees

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Running Title: Familial and Nonfamilial Morbid Obesity

Supported by NIH Grant DK44655

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Abstract

In view of increased mortality and morbidity among individuals with morbid obesity, many avenues are being pursued to discover causal related mechanisms for this disorder. This study examined the question of whether or not anthropometric and biochemical measures of morbidly obese subjects are expressed differently in familial morbidly obese probands (probands with at least one other morbidly obese first degree relative) versus nonfamilial probands (only one member of family with morbid obesity). Subjects included 92 familial morbidly obese probands (58 female; 34 male) and 59 nonfamilial morbidly obese probands (44 female; 15 male). In addition to measurement of blood pressure, a number of anthropometric and biochemical variables were measured, including percent body fat, insulin, blood lipids and urine catecholamines. Based upon statistical comparison of the two morbid obesity groups, there were no significant differences between familial and nonfamilial probands in anthropometric measurements. Likewise, biochemical measures were essentially the same in both the familial and nonfamilial probands. These findings suggest that the characteristics related to morbid obesity are the same for familial and nonfamilial probands, and that morbid obesity is likely the result of a familial trait.

INDEX TERMS: Genetics, Body Weight, Body Mass Index, Obesity

Introduction

The incidence of both obesity and overweight in the United States has increased strikingly over the past 30 years (15). While many health risk indicators such as blood pressure, blood cholesterol, coronary heart disease and stroke are declining in prevalence in the U.S., initial findings from NHANES III data (Phase 1:1988-1991) reveal that the incidence of overweight (body mass index, BMI) has increased by 8 percent (5,7,11). Although unclear what correlation might exist between the significant increase in BMI and mortality/morbidity risk, there remains a certainty regarding the current major risk of morbid obesity on early disability and death. Morbidly obese men have a twelve times increased mortality rate and morbidly obese women have a six times increased mortality rate when compared to normal weight men and women (3). In addition, morbid obesity significantly increases the risk for hypertension, atherosclerosis, diabetes, gallbladder disease, lipid disorders, operative risk, pulmonary dysfunction and some forms of cancer (2,8,9,13).

In view of the increased mortality and morbidity risk associated with morbid obesity, efforts have been directed to discover causal related mechanisms for morbid obesity. To further these efforts, this investigation explored the question of whether or not anthropometric and biochemical variables of morbidly obese subjects are expressed differently in familial morbidly obese probands (probands with <u>at least one</u> other morbidly obese first degree relative)

versus nonfamilial probands (probands without any morbidly obese first degree relatives). By comparing obesity-related phenotypes of familial versus nonfamilial morbidly obese probands we hoped to identify specific differences that may be possibly linked to genetic variation.

Methods

Subjects. All morbidly obese probands in this study met the criteria for morbid obesity. Using a classification of Wadden, morbid obesity was defined as greater than 100 pounds or 100% over ideal weight (12). Ideal weight was determined from the Metropolitan Life Insurance Tables of 1983 after measuring elbow breadth in clinic. (This degree of obesity is approximately equal to a BMI of 45 or greater (2). Subjects were classified as familial if they had at least one other morbidly obese first degree relative and as nonfamilial if they had no other morbidly obese first degree relative. One-hundred-and-two morbidly obese females (58 familial; 44 nonfamilial) and 49 morbidly obese males (34 familial; 15 nonfamilial) were recruited for participation in this study.

Recruitment of Subjects. Subjects were recruited from two sources. The first source was identified from a population-based family history database of over 100,000 families. Data were collected from Health Family Tree questionnaires, which are detailed family histories completed by high school students and their parents as part of the Utah school curriculum (6,14). Fifty-four out of the 55 high schools along the Wasatch Front (within a 50 mile radius of Salt Lake City) participate in this program. There is little difference in participation rates between schools in rural versus urban areas or between high and low income areas. Health information reported by the families includes the report of "usual weight" categorized as: slender or average; 10-49 pounds overweight; 50-99

pounds overweight; or over 100 pounds overweight.

A random sample of individuals identified as being "over 100 pounds overweight" was sent introductory letters and then contacted by telephone to verify the Health Family Tree record and to ascertain their interest as a participant in the study.

The second source of subjects were participating in a very-low-calorie diet, weight-loss program (Optifast, Sandoz Nutrition) operating at 4 different hospitals in Utah. The directors of the respective weight-loss clinics obtained permission from program participants prior to their being contacted for research participation. Individuals giving consent were then recruited by telephone or in person. Additional recruitment detail has previously been described (1).

Data Collection. The majority of data collection occurred at the Cardiovascular Genetics Research Clinic, University of Utah. Prior to the clinic visit, participants were asked to collect a 24-hour urine sample. The 24-hour urine collection was used for measurement of urine catecholamine levels (norepinephrine, epinephrine, dopamine and creatinine) and for storage for later biochemical testing.

Prior to clinic participation, consent forms were signed by subjects. The clinic visit consisted of a 12-hour fasting venous blood draw from which the following biochemical variables were measured: standard 20-channel blood chemistry, plasma insulin, and a lipid profile (total-cholesterol, HDL-cholesterol,

measured LDL-cholesterol, VLDL-cholesterol and triglycerides).

Anthropometric measurements were taken following the blood draw. Height was measured with a Harpenden anthropometer (Holtain Ltd). Weight was measured with a Scaletronix scale which weighs up to 364 kg (800 pounds). Greatest weight was self-reported. The following circumferences were measured with a Lufkin metal tape: Waist, measured at the midpoint between the lowest rib and the iliac crest; Hip, measured at the largest circumference over the buttocks; Upper arm, measured at the midpoint between the acromial and the olecranon processes; and Calf, measured at the largest circumference. Width measurements, measured in millimeters with a sliding caliper, included: Elbow, measured between the medial epicondyle and the lateral epicondyle of the humerus with the elbow flexed at ninety degrees; and Knee, measured between the condyles of the femur with the knee in a flexed position.

Bioelectrical impedance (RJL Systems Analyzer, Body Comp 11.V1 program) was used to measure percent body fat. Subjects were instructed to fast 12 hours prior to the measurement. Furthermore, subjects were asked not to exercise or consume alcohol for at least 24 hours prior to the measurement, and subjects were asked to report to the lab in a balanced hydration state. Techniques used for body placement, skin preparation and electrode placement were based upon those recommended in the RJL Technical Manual.

Blood pressure was measured by a standard mercury sphygmomanometer

using the 1st and 5th phase Korotkoff sounds. After 5 minutes of rest and in the sitting position, the mean of two measurements from the right arm was obtained. Measurements were taken until they were within 10 mm Hg (both systolic and diastolic blood pressure). Proper cuff size was used for each participant.

Statistical Analysis. Analysis of covariance was used to compare probands with familial obesity to probands with nonfamilial obesity. Mean differences were compared between the two groups for the continuous variables of interest, with proband type, gender, age and other possibly confounding variables as covariates.

Results

Nonfamilial Families. Using the Health Family Tree database, (data collected between Spring of 1988 and Spring of 1995), 739 nonfamilial families were identified. Two-hundred-and-eleven (211) families were excluded from the 739 for the following reasons: Because of overlap participation with other studies (do to policy of certain granting agencies, some families already participating in studies were not permitted to become involved in the obesity research); due to families having been entered twice in the system because of two siblings completing Health Family Trees in different years (names were not obtained to detect duplicates until contact was made with the families); or because a parent did not give consent for further contact. Of the 528 families remaining, 172 of them had one or more sibling 50-99 pounds overweight. Two-hundred-twenty-five (225) families had one or more siblings 30-50 pounds overweight. Therefore, of the original 739 nonfamilial families identified, only 131 met the nonfamilial criteria (one sibling 100 pounds overweight with the remaining siblings and parents of average weight).

Eighteen (18) of the nonfamilial families identified from the family trees as meeting our criteria were found to have another morbidly obese sibling upon telephone verification, and 17 probands were determined not to be 100 pounds overweight. Additional reasons for potential nonfamilial families not participating in the study included: Three probands were adopted and had no

knowledge of their biologic parents and siblings; thirty probands chose not to participate; and 20 probands were deleted because of death and inability to locate for participation. Therefore, of 528 potential nonfamilial families, 485 (91.9%) were deleted for above stated reasons.

Familial Families. Using the Family Health Tree database (data collected between Spring of 1986 and Spring of 1995), 401 familial families were identified. Ninety-one (91) families were excluded from the 401 for the following reasons: Because of overlap participation with other studies; due to families having been entered twice into the system; and because a parent did not give consent for further participation. Of the 310 families remaining, 15 probands were determined not to be 100 pounds overweight. Five families were deleted because they did not meet the study criteria after examining the Health Family Tree. Additional reasons for potential familial families not participating in the study included: Twenty-five (25) probands chose not to participate; Eight (8) familial families could not be located; One (1) proband was adopted; and 2 probands were deceased. Therefore, of the 310 potential familial families, 56 (18.1%) were deleted for above stated reasons.

Anthropometric and Biochemical Variables. Detailed in Table 1 and 2 are the characteristics and mean anthropometric data of the familial and nonfamilial morbidly obese probands (Table 1 for females; Table 2 for males). There was no statistical difference in age between the familial and nonfamilial probands

(male and female). The severity or degree of the obesity (determined by such variables as weight, greatest weight, BMI, and percent body fat) were statistically similar between the familial and nonfamilial probands for both the male and female groups, as were fat distribution patterns (determined by circumference measurements). Body frame size or bone size, measured by both elbow and knee widths, likewise, were not statistically different (familial versus nonfamilial).

Detailed in Tables 3 and 4 are the biochemical measures, blood pressure and resting heart rate for the familial and nonfamilial morbidly obese probands (Table 3, Female; Table 4, Male). There were no significant differences in the urine catecholamine levels (norepinephrine, epinephrine, dopamine and creatine), between familial and nonfamilial female probands. Likewise, the urine catecholamine levels were not significantly different between the male familial and nonfamilial probands with the exception of epinephrine (familial = 7.7; nonfamilial = 10.7; $p<0.003$). All other biochemical indices measured such as cholesterol, insulin and glucose were similar in the familial and the nonfamilial morbidly obese male and female probands.

With reference to blood pressure and resting heart rate there were no significant differences in these variables between the female familial and nonfamilial subjects but there was a significant difference in diastolic blood pressure between the male familial and nonfamilial groups (familial = 79.1;

nonfamilial = 87.3; $p<0.04$).

Discussion

Morbid obesity occurs in approximately 1-2 percent of the population. Whether morbid obesity represents only an extreme of a continuous obesity distribution or whether there are specific genetic and environmental processes that are responsible for this severe obesity, as is the case for familial hypercholesterolemia and LDL cholesterol, is unknown. In a previous study, our laboratory showed strong familial aggregation for morbid obesity, with 48% of the morbidly obese probands having one or more first-degree relatives who were also morbidly obese (1).

In an effort to gain additional clues to this question, this study was undertaken to measure physical and biochemical characteristics of morbidly obese subjects whose family history with reference to obesity is varied. The central question asked was whether or not the mechanism for the development of morbid obesity is the same in familial versus nonfamilial families. If it is assumed that familial families have a genetic predisposition to environmental insults, then one might expect different biochemical or anthropometric profiles between the groups, hinting at an underlying mechanism. On the other hand, it can be argued that the nonfamilial families are merely those families who might have a genetic predisposition but only one sibling inherited the gene. Or, familial families may actually include persons without a genetic predisposition but who share the same environmental factor leading to obesity. This last

statement is less likely because of the overfeeding experiments that suggest persons only gain so much weight and then plateau (4,10). It would appear, therefore, very difficult to become morbidly obese merely through environmental factors without the genetic predisposition.

Based upon the comparison of biochemical and anthropometric variables between the familial and nonfamilial probands there were essentially no statistical differences. The two exceptions were found among the male familial versus nonfamilial group. Urine epinephrine and diastolic blood pressure were significantly less among the familial probands in comparison to the nonfamilial probands. Our feeling is that the significant difference in epinephrine likely did not represent a true difference due to the smaller sample size among the male morbidly obese probands. We found fewer of the male probands willing to collect a 24-hour urine sample, (only fifty percent of the male familial subjects participated in the urine collection). The diastolic blood pressure difference between male familial and nonfamilial probands was only slightly significant ($p<0.04$). Further analysis of an additional diastolic blood pressure reading among the two groups showed no significant differences (familial = 81.5; nonfamilial = 99.8; $p<0.06$). The virtual similarity between familial and nonfamilial morbidly obese subjects would suggest that regardless of the reason for weight gain, the gross physiologic response to that weight gain appears to be similar among groups. In addition, on average the weight appears to be

regionally deposited in a similar manner between groups, and any association between the regional adiposity and biochemical measures such as lipids, glucose and insulin appear to be identical.

As previously reviewed, final ascertainment of nonfamilial families was much more difficult than the ascertainment of familial families. Often, what appeared to be a nonfamilial family, based upon the initial Family Health Tree data, was in reality a familial family when actual contact with the family was made. The nonfamilial families that ultimately qualified for the study and were actually ascertained for data aquisition represented only 8.1 percent of the total initial nonfamilial data pool. By comparison, the familial families who were ultimately ascertained for the study represented 81.9 percent of the initial nonfamilial data pool.

In conclusion, the results of this study suggest that the characteristics related to the morbid obesity are the same for familial probands compared to nonfamilial probands. There may exist, however, differences between these two groups in biochemical measures of tissues or organs not measured in this study. This study seems to support the hypothesis that morbid obesity is likely the result of a familial trait and that nonfamilial families represent families who may have a genetic predisposition to excessive obesity with only one sibling inheriting or expressing the gene. There exists also the possibility that more extensive ascertainment of the nonfamilial family beyond first degree relatives

to include cousins of the proband would reveal additional morbidly obese family members, suggesting that in actuality there may be no "nonfamilial" morbidly obese families.

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APPENDIX 12
EFFECT SIZE INDEX

Effect Size Index = ABS (Mean X1 - Mean X2)/
SQRT (((N1 -1) * (SD1)*(SD1) + (N2 -1)*(SD2)*(SD2)/ (N1 + N2 -2)))

Aggregating vs. Non-Aggregating Severely Obese Subjects

	Mean X1	Mean X2	N1	SD1	N2	SD2
0.003	2158.1	2182.1	85	1019	52	630.3
0.0212	16.3	17.8	85	7.7	52	5.6
0.0311	32	34	85	7	52	6
0.0000	19	19	85	6	52	5
0.0541	13	15	85	4	52	6
0	12	12	85	3	52	3
0.0362	12	13	85	3	52	3
0.0121	50	49	85	9	52	8
0	18	18	85	4	52	3
0.0047	46.4	45.3	85	25.3	52	18.1
0.0218	32.3	36.3	85	20	52	15.3
0.0034	28.5	29	85	16.2	52	10
0.0068	29.8	30.8	85	16.1	52	10.2
0.0007	270.7	271.6	85	138.9	52	92.7
0.007	21	21.6	85	9.5	52	9.1
0.0218	3.8	3.5	85	1.5	52	1.3
0.0042	96.2	97.8	85	41.9	52	31.2
0.0056	83.3	90.3	85	136.2	52	104.5
0.0419	18.3	33.1	85	38.4	52	48.8
0.0113	1.4	0.6	85	7.7	52	2
0.0099	0.054	0.005	92	0.519	53	0.013
0.0020	2,006	2016	89	521	52	516
0.0228	566	653	89	407	52	388
0.0288	15.3	16.6	89	4.8	52	4.6
0.0273	4.5	5.4	89	3.5	52	3.3
0.0070	5.9	6.5	92	9	53	8
0.0261	1.6	1.8	92	0.8	53	0.8
0.0681	3.7	6	92	3.5	53	7
0.0201	1.2	1.7	92	2.6	53	2.2
0.0065	2.8	2.9	92	1.6	53	1.8
0.0065	7.8	7.7	92	1.6	53	1.5
0.0052	8.3	8.4	92	2	53	1.7
0.0034	5.7	5.6	92	3.1	53	3.1
0.0209	5.7	6.3	92	3	53	3
0.0065	6.1	6.3	92	3.2	53	3.5
0.0161	4.7	4.3	92	2.6	53	2.5
0.0067	3.4	3.6	92	3.1	53	3.5
0.0187	3.8	4.3	92	2.8	53	2.8
0.0087	0.6	0.5	92	1.2	53	0.7
0.0185	0.9	0.6	92	1.7	53	0.9
0.0147	53.2	56.2	92	21.3	53	20.8

0.0220	61.1	65.1	92	19	53	21.2
0.0060	70.9	68.8	92	36.7	53	47.1
0.0253	60.8	66.3	92	22.7	53	26.1
0.0031	59.8	61	92	40.8	53	46.5
0.0099	73.1	75.6	92	26.5	53	22.2
0.0191	42.7	39.1	92	19.7	53	20.2
0	68.5	68.5	92	20.7	53	21.1

Aggregating vs. Non-Aggregating Normal Weight Subjects

	Mean X1	Mean X2	N1	SD1	N2	SD2
0.0306	1774.3	1955.7	87	639.4	52	592
0.0867	23.7	30.4	87	8.3	52	9.9
0.0134	29	30	87	8	52	7
0.0179	16	17	87	6	52	6
0	13	13	87	4	52	5
0	11	11	87	3	52	3
0	11	11	87	3	52	3
0.0098	54	53	87	11	52	9
0.0357	17	18	87	3	52	4
0.0401	31.9	38.2	87	16.9	52	17.7
0.0104	26	27.3	87	13.4	52	11.9
0.0306	20.7	23.6	87	10.2	52	9.6
0.0306	21.3	24.4	87	10.9	52	8.5
0.0208	237.5	256	87	95.8	52	84
0.0011	19.9	19.8	87	9.9	52	6.9
0.0154	4.8	4.4	87	2.8	52	2.5
0.0336	75.4	84.3	87	28.5	52	29.4
0.0016	147.5	144.2	87	216.1	52	211.3
0.0347	21.6	7.9	87	42.5	52	18.2
0.0048	4.8	5.4	87	13.3	52	14.8
0.0237	0.0013	0.0047	92	0.015	52	0.014
0.0323	1716	1539	85	598	52	470
0.0094	590	636	85	533	52	392
0.0096	22.9	23.6	85	7.9	52	8
0.0825	5.7	9.8	85	5.4	52	6
0.0241	13.6	9.6	92	17.4	52	9.9
0	2.2	2.2	92	0.8	52	0.9
0.0046	7.3	7	92	6.8	52	5.5
0.0136	1.9	2.2	92	2.3	52	2
0.0156	4.1	4.4	92	2	52	2.5
0.0209	1.7	1.6	92	0.5	52	0.6
0.0165	7.2	7.5	92	1.9	52	2
0.0238	7.5	8	92	2.2	52	2
0.0663	5.7	3.8	92	3	52	2.3
0.0200	4.2	3.7	92	2.6	52	4.1
0.0030	6.1	6.2	92	3.5	52	3.3
0.0201	4.6	5.1	92	2.6	52	2.8
0.0070	3.9	4.1	92	3	52	2.8
0.0252	4.5	5.2	92	2.9	52	2.5

0.0401	1	1.5	92	1.3	52	1.8
0.0348	1.4	1.9	92	1.5	52	1.9
0.0218	77.1	80.2	89	15.1	52	19.1
0.0212	72.9	76.7	89	19.1	52	18.8
0.0081	81	84.2	92	41.2	53	36.8
0.0093	87.6	89.1	92	16.8	53	26.5
0.0307	90.4	83.6	92	23.1	53	37.3
0.0136	85.9	88.9	90	23.3	52	20.2
0.0165	61.7	64.6	90	18.6	52	22.2
0.0277	75	78.8	89	14.6	52	11.3

Mean Intrapair Differences of Aggregating & Non-Aggregating SO and NW Sibs

	Mean X1	Mean X2	N1	SD1	N2	SD2
0.0179	416.2	240.6	81	1096.1	50	800.7
0.0229	-7	-9.1	81	10.2	50	10.4
0	3	3	81	8	50	8
0.0397	3	0.5	81	7	50	8
0.0623	0.2	3	81	5	50	6
0.0111	1	0.7	81	3	50	4
0	1	1	81	4	50	3
0	-3	-3	81	11	50	10
0.0223	0.9	0.1	81	4	50	4
0.1279	14.4	47.1	81	28.5	50	27.9
0.0020	7.1	7.5	81	22.1	50	19.5
0.0250	7.8	3.9	81	17.4	50	14.4
0.0208	8.8	5.4	81	18.2	50	14.7
0.0135	39.2	21.2	81	148.7	50	112.9
0.0057	1.1	0.5	81	11.8	50	11
0.0159	-1	-0.6	81	2.8	50	1.7
0.0193	21.6	13.1	81	49.1	50	38.9
0.0021	-52.8	-48.4	81	229.4	50	239.7
0.0338	-2.3	15.9	81	60.1	50	63.1
0.0077	-3.5	-2.5	81	14.4	50	13.5
0.0101	0.06	0.01	92	0.52	53	0.02
0.0151	269	374	83	766	50	623
0.0147	16	88	83	541	50	519
0.0142	-7.8	-6.6	83	9.3	50	6.8
0.0053	-2.8	-2.5	83	6.2	50	5.9
0.0143	-7.8	-5.1	92	19.7	53	19.6
0.0190	-0.8	-0.6	92	1.1	53	1.2
0.0135	-3.5	-2.5	92	7.7	53	11.1
0.0031	-0.7	-0.8	92	3.4	53	3.6
0.0167	-1.4	-1	92	2.5	53	2.7
0.0262	0.5	-0.1	92	2.4	53	1.7
0.0105	0.8	0.5	92	3	53	2.4
0.0199	1.5	0.7	92	4.2	53	4.4
0.0100	1.4	1.8	92	4.2	53	3.7
0.0122	0.05	0.6	92	4.7	53	4.2
0.0029	0.2	0.1	92	3.6	53	3.1

0.0194	-0.5	0.3	92	4.3	53	4.5
0.0110	-0.7	-0.3	92	3.8	53	3.7
0.0330	-0.5	-1.1	92	1.9	53	2.3
0.0349	-0.4	-1.2	92	2.4	53	2.1
0.0152	-23.8	-20.4	89	23.8	50	22.6
0.0078	-12	-10.1	89	25.9	51	27.3
0.0082	-10.1	-14.3	92	53.4	53	51.6
0.0057	-26.9	-25.4	92	27.5	53	29.1
0.0128	-30.6	-25.7	92	40.1	53	51.7
0.0016	-13.3	-12.8	90	34.1	51	27.6
0.0025	-19.5	-18.9	90	25.4	51	24.4
0.0068	-6.4	-8	89	24.9	51	23.8

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