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Metabolic Syndrome: Fact or Fiction

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Metabolic syndrome is a highly debated condition which has been defined to serve as a predictor for cardiovascular disease (CVD) and type 2 diabetes. Persons with metabolic syndrome may be 9 to 30 times more likely to be diagnosed with type 2 diabetes and 2 to 4 times more likely to develop CVD [1]. Although research studies have proven links between the conditions that comprise metabolic syndrome and risk for CVD and type 2 diabetes, some skeptics argue this syndrome does not really exist [2,3].

The American Diabetes Association has raised questions of the validity of metabolic syndrome because the underlying cause is not known. Despite these concerns, in 2006, the International Diabetes Federation (IDF) issued a worldwide definition of metabolic syndrome that includes different measures

based on ethnicity, which was where previous definitions fell short [2]. For the criteria for metabolic syndrome, refer to Table 1.

Ford et al. published findings from the first prevalence study to estimate metabolic syndrome in the adult population [4]. The criteria used to identify metabolic syndrome was issued by the National Cholesterol Education Program Adult Treatment Panel (ATP

III). These criteria are similar to the criteria issued by IDF, but do not take into account waist circumference measurements for different ethnic groups. Ford et al. found that the age-adjusted rate for metabolic syndrome was 24% in adults 20 years old or older. Similarly, the National Heart, Lung, and Blood Institute reports nearly 25% of adults in the U.S. have metabolic syndrome. Almost 45% of adults in the Ford

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Table 1: IDF Criteria for Metabolic Syndrome	
Central obesity (waist circumference with ethnicity specificity*)	
Plus two or more of the following criteria:	
Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Raised blood pressure	systolic BP ≥130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose	(FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes recommended but is not necessary to define presence of the syndrome
*Europeans- Men ≥94 cm, Women ≥ 80cm; South Asians- Men ≥90cm, Women ≥80cm; Chinese- Men ≥90cm, Women ≥80cm; Japanese Men ≥85cm, Women, ≥90cm; Sub-Saharan Africans- more data needed.	

Multiple Pair-Wise Comparisons

BY: CHARLES G. MINARD, PhD

Many studies seek to test multiple hypotheses about a population from a single sample. For instance, approximately 19,000 genes in human liver cells were screened in a study by Clement et al.[1] to identify genes that were over- or under-expressed in a simulated microgravity environment. The level of expression of each gene was quantified through microarray analysis, and a t-test was performed for each gene. This presents some interesting statistical issues, particularly with respect to genomic studies.

Researchers often assume an $\alpha = 0.05$ level of significance for each hypothesis test. This value is often selected because everyone else does, and it has become synonymous with statistical significance. The selection of 0.05 has roots that lie with a publication by R.A. Fisher[2] in which he stated that

If the difference is many times greater than the standard error, it is certainly significant, and it is a convenient convention to take twice the standard error as the limit of significance; this is roughly equivalent to the corresponding limit $P=0.05$. . . (Fisher 1925)

However, the level of significance should be more thoughtfully measured in practice. Consider a more simplistic situation than Clement et al. in which the expression of only two genes is studied. Assuming an $\alpha = 0.05$ level of significance, then the probability of committing a Type-1 error is 0.05. Type-1 error is defined as the probability of a false positive result. This is as opposed to the aptly named Type-2 error that describes the probability of false negative results and is used in power calculations to determine sample size. If a hypothesis test is performed for each gene and statistical significance is evaluated at the 0.05 level of significance, then

the probability of getting a false positive result is

$$\begin{aligned} \text{Pr (Type-1 error)} &= \text{Pr (Type-1 error gene 1)} + \text{Pr (Type-1 error} \\ &\quad \text{gene 2)} - \text{Pr (Type-1 error gene 1 \& 2)} \\ &= 0.05 + 0.05 - (0.05)^2 \\ &= 0.0975 \end{aligned}$$

The overall Type-1 error rate is 0.0975 (not 0.05), and the researcher is more likely to obtain a false positive result. The comparison-wise Type-1 error rate for each gene is 0.05; however, the experiment-wise Type-1 error rate is inflated. The researcher will be more likely to obtain a statistically significant result as the number of pair-wise comparisons increases if the level of significance is not controlled.

The Bonferroni correction is a simple method that may be used to appropriately adjust the level of significance value. If N pair-wise comparisons are to be made assuming an experiment-wise level of significance α_e , then

$$\alpha_c = \frac{\alpha_e}{N}$$

gives the comparison-wise level of significance α_c for each hypothesis test. In our example with two genes

$$\alpha_c = \frac{0.05}{2} = 0.025$$

and only p-values less than or equal to 0.025 would be declared statistically significant.

Controlling the Type-1 error rate for multiple pair-wise comparisons is important to appropriately analyze research results. The Bonferroni correction is a simple method for controlling the error rate and it is easily implemented. Other, more sophisticated techniques include the Tukey, Newman-Keuls, Dunnett, Scheffé, and nonparametric procedures.

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et al. study in the age-range of 50 to 69 years met the metabolic syndrome criteria, which follows the notion that increased age is a risk factor for developing metabolic syndrome. African Americans and Mexican Americans were also found to be disproportionately affected by this syndrome.

Metabolic syndrome is present in about 5% of people with normal body weight, 22% of people who are overweight, and 60% of people considered obese [5]. Adults who consistently gain 5 or more pounds per year raise their risk of developing metabolic syndrome by up to 45%. While obesity itself is likely the greatest risk factor, other factors of concern include: women who are postmenopausal, smoking, eating an excessively high carbohydrate diet, lack of activity, and consuming an alcohol-free diet.

Perhaps the most interesting aspect of metabolic syndrome is that it can be prevented. By making lifestyle changes, people with metabolic syndrome can decrease their risk for CVD and type 2 diabetes. The most commonly cited management strategies for the syndrome are weight loss

and increased physical activity. Changing dietary intake is another way to manage metabolic syndrome. More research is needed in this area to try to identify causes of metabolic syndrome, to understand the effects of metabolic syndrome on different ethnic groups and genders, and to come to a consensus if this is actually a syndrome. ■

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The example by Clement et al., however, provides a somewhat extreme example of multiple pair-wise testing. The Bonferroni correction would require an $\alpha = 0.0000026$ level of significance for each gene assuming 19,000 genes were tested. Genetic studies often use other methods for controlling the Type-1 error rate such as false discovery rate (FDR) control [3]. Clement et al. controlled the Type-1 error rate by letting $\alpha = 0.01$ and imposing minimum restrictions on the magnitude of gene regulation. ■

Chronic Diseases Surveillance: What is it and who conducts it?

BY: MELISSA HALM, MPH

Chronic diseases began to replace infectious diseases as the most common causes of death in the early 20th century. This substantial decrease in infectious disease mortality was attributed to the development of better sanitation practices, advancements in medicine and health care, and life style changes. In 2005, the Centers of Disease Control and Prevention (CDC) reported that the 3 leading causes of mortality in the United States were attributed to chronic diseases [1]. These 3 causes of death included diseases of the heart, cancer, and cerebrovascular diseases [1]. With the reality of this growing health problem, health departments have begun to focus more resources into chronic disease surveillance.

Health departments typically conduct disease surveillance activities through local, state, and federal mandates that require health care and laboratory personnel to report specific conditions to the local health authority within a specific time period. These mandates were developed to prevent the spread of communicable diseases and health-related threats in the community. In the state of Texas, 76 conditions are reportable to the local health authority [2]. These conditions include infectious diseases, environmental exposures, work-related exposures, traumatic injuries, and one chronic disease. Cancer is the only chronic disease reportable under the current notifiable conditions list [2]. Most of the reportable conditions are infectious diseases.

Health department surveillance systems are well equipped for in-

fectious disease surveillance, but how about chronic disease surveillance?

Currently, chronic disease surveillance activities are performed primarily by state and federal health departments. Few local health departments have the resources to extend their disease surveillance activities to chronic diseases. State and federal health departments use different surveillance techniques to collect information about patients with chronic disease. Common chronic disease data collection techniques include disease registries, hospital discharge data, mortality surveillance, randomized population-based telephone interviews questioning citizens on a myriad of health related issues, and youth behavioral surveys [3, 4].

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Disease Registries [3, 4]: Disease registries gather patient information for specific diseases or disease groups, like cancer. These registries contain basic demographic, diagnosis, and treatment information for patients. The registries are useful tools for determining the incidence and prevalence rates of diseases. For more information regarding incidence and prevalence rates, refer to Table 2.

Hospital Discharge Data [3, 4]: State-licensed hospitals provide patient discharge information to the state health departments. The state health departments specify the patient information required to be reported. Like disease registries, the patient information reported to the state health department is limited to basic demographic data, diagnosis, and treatment information.

Mortality Surveillance [3, 4]: Local health departments are responsible for collecting the death records for their jurisdictions and subsequently forwarding the death records to the state health department. The local health departments use state standardized death record forms. These forms contain demographic information, birth and death information, cause(s) of death, and underlying conditions.

Behavioral Risk Factor Surveillance System (BRFSS) [3, 4]: BRFSS is an ongoing randomized population-based telephone survey that collects nationally standardized information on numerous health-related issues. Participants must be 18 years of age or older. Health-related issues collected in this survey include behaviors, chronic and infectious diseases, and injuries. BRFSS provides state health departments with the ability to collect and analyze their own data, as well as compare their results to other states and national results. BRFSS also acts as a repository for data. Local health departments and research institutions can request de-identified data for their own analytical needs.

Youth Risk Behavior Surveillance System (YRBSS) [3, 4]: YRBSS is a school based survey, similar to BRFSS, that focuses on high school students. Surveys collect information on participant's behaviors and injuries.

Chronic diseases are a growing concern throughout the United States. Chronic disease surveillance and subsequent analysis are necessary for providing information to public health officials and health care providers. Public health officials can use this information to implement prevention programs and policies. Health care providers can use this information to determine risk factors and treatment options for their patients. ■

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Table 2: Incidence and Prevalence Rates

$$\text{Incidence rate} = \frac{\text{Number of new cases of a disease}}{\text{Number of individuals in the at risk population}} \times \text{Time}$$

$$\text{Prevalence rate} = \frac{\text{Number of old and new cases of a disease}}{\text{Number of individuals in the at risk population}} \times \text{Time}$$