

Menopause is a normal, natural event—defined as the final menstrual period (FMP). It represents the permanent cessation of menses resulting from loss of ovarian follicular function usually due to aging. Menopause can occur naturally (spontaneously)—occurring on average around age 51—or be induced through a medical intervention (surgery, chemotherapy, or pelvic radiation therapy).

Aging is the natural progression of changes in structure and function that occur with the passage of time in the absence of known disease. Aging of the female reproductive system begins at birth and proceeds as a continuum. It consists of a steady loss of oocytes from atresia or ovulation, and does not necessarily occur at a constant rate. Because of the relatively wide age range (40-58 y) for natural menopause, chronologic age is a poor indicator of the beginning or the end of the menopause transition.

Menopause affects every woman. And, as the large baby-boom generation reaches midlife and beyond, an unprecedented number of women are now postmenopausal. An estimated 6,000 US women reach menopause every day (over 2 million per year). In addition, more women are living beyond age 65. A woman's life expectancy in the Western world is estimated at 79.7 years. Today, a woman who reaches age 54 can expect to reach age 84.3. About two thirds of the total US population is expected to survive to age 85 or longer.

During the transition from the reproductive years through menopause and beyond, a woman experiences many physical changes, most of which are normal consequences of both menopause and aging. Some of the physical changes observed around menopause may be signs of illness that develop during midlife, such as diabetes. Sometimes, health problems arise when changing hormone levels and the physical effects of aging are coupled with an individual's genetic makeup, certain unhealthy lifestyles, and/or other stresses of midlife.

Survey research does not verify the concept of a “midlife crisis” as universal or even widely present in the general population. However, women in midlife may fear aging for a variety of reasons, some of which are universal, some peculiar to their culture, and the rest reflecting their personal and family circumstances. Women at midlife may be reacting to a multitude of changes that are common at this time of life, such as financial, relationship, and caregiving burdens, that can elicit fear and anxiety.

All women experience menopause, but each one does so in a unique way. How a woman responds to the physical changes of menopause may be similar to the way her mother responded, although the evidence to support this notion is limited.

Lifestyle, demographic factors, and attitudes all influence a woman's perception of menopause. The menopause

experience is often perceived as merely the cessation of menses. A woman may view the end of fertility as liberation from the possibility of pregnancy, or she may grieve for the children she never had. For women who have had an unexpected early menopause, either natural or induced, their experience may be more negative. The level of menopause-related symptoms will also have an influence. Some women will have troublesome symptoms, whereas others may navigate the transition with few or even no symptoms at all.

Diverse social and cultural differences can also affect a woman's experience of menopause and her view of menopause treatments as well as her overall health and well-being. Risk factors, patterns of disease and mortality, access to health care, economic status, existing medical therapies, and societal norms related to femininity and aging all differ across groups of women. There is very little research on how these differences affect the experience of menopause. To date, menopause research has focused mostly on middle-class white women. Although different populations are now being studied, considerable information is needed before many aspects of menopause are better understood.

In one study, 80% of women experiencing menopause reported no decrease in quality of life (QOL), and 75% of the women denied experiencing any loss in their attractiveness. Most women (62%) reported positive attitudes toward menopause itself. In another study, most women viewed menopause as inconsequential, and suggested that other events of midlife were more important or stressful. A cohort of well-educated, midlife women described the menopause transition as a normal developmental event. Only about 10% of peri- and postmenopausal women participating in community-based studies reported feelings of despair, irritability, or fatigue during the menopause transition.

The QOL and health status of a generally low-income and poorly educated population of menopause-aged women were examined in a cross-sectional study. Women who were employed, had attained higher levels of education, or had higher levels of income reported better overall health and fewer menopausal symptoms. There were no significant differences between ethnic groups with respect to either menopausal QOL or health status. The surgical intervention of hysterectomy (with bilateral oophorectomy) did not appear to be a factor in decreasing QOL. Compared with women with an intact uterus, women who underwent hysterectomy expressed more improvement, especially in the areas of sexual relationships, spouse or partner relationships, personal fulfillment, and physical health. This improvement did not appear to be the result of menopausal hormone therapy (HT).

Most US postmenopausal women (51%) surveyed in a 1998 NAMS-sponsored Gallup Poll reported being happiest and most fulfilled between ages 50 and 65 compared with when they were in their 20s (10%), 30s (17%), or 40s (16%). Many women reported improvement in various areas of their

lives since menopause. They reported a sense of personal fulfillment, an ability to focus on hobbies or other interests, and improved relationships with their spouse or partner and with friends. A majority (51%) said their sexual relationships had remained unchanged. Lifestyle behavioral changes were often initiated during this midlife period.

Fortunately, menopause is now better understood and more openly discussed than ever before. Menopause can be viewed as a sentinel event that presents a unique opportunity for women, working with their healthcare providers, to evaluate personal health and improve health practices. Collaboration between the woman and her provider, characterized by mutual respect and trust, is the goal of menopause counseling. Menopause counseling can facilitate informed decision making and validate the woman's confidence in her decisions, and in her ability to carry them out or modify them over time. Individualized screening and management approaches are essential components of this collaboration.

Accurate information about physiologic changes, management of menopause symptoms, and reducing disease risk is essential. Although menopause is perhaps the most obvious physical event, general knowledge about the aging process is also needed. Additionally, psychological support may be required for the many psychosocial issues women encounter in midlife.

By considering a woman's preferences, values, and concerns, the menopause practitioner will enhance the woman's sense of well-being, not only around menopause but for the rest of her life.

**Terminology**

Clinicians and researchers in the field of menopause have long recognized the need for universally accepted menopause terminology as well as a staging system useful in categorizing the last 10 to 15 years of reproductive aging. In 2001, the Stages of Reproductive Aging Workshop (STRAW), sponsored by The North American Menopause Society (NAMS), the National Institutes of Health, the American Society for Reproductive Medicine, and the National Institute of Child Health and Human Development, addressed nomenclature and a staging system. Previously, the Council of Affiliated Menopause Societies (CAMS), an international policy organ of the International Menopause Society, had developed standardized definitions for menopause-related events. Although STRAW redefined some terms, other CAMS terms remain in use.

The reproductive aging continuum created by STRAW is divided into seven stages: five precede and two follow the FMP (see Fig. 1). STRAW points out, however, that not all healthy women will follow this pattern; some will seesaw between stages or skip a stage altogether.

**Menopause.** As defined by STRAW, *menopause* (ie, "spontaneous" or "natural" menopause) is recognized to have occurred after 12 months of amenorrhea with no obvious pathologic cause. It reflects a near-complete but natural diminution of ovarian hormone secretion. There is no adequate independent biological marker for menopause.

Menopause is one point in time. The phrases "in menopause" and "going through menopause" are

**Figure 1. Stages/nomenclature of normal reproductive aging in women**

	Final Menstrual Period (FMP)							
	-5	-4	-3	-2	-1	0	+1	+2
<b>Terminology:</b>	Reproductive			Menopausal Transition		Postmenopause		
	Early	Peak	Late	Early	Late*	Early*	Late*	
				Perimenopause				
<b>Duration of Stage:</b>	variable			variable		Ⓐ 1 yr	Ⓑ 4 yrs	until demise
<b>Menstrual Cycles:</b>	variable to regular	regular		variable cycle length (>7 days different from normal)	≥2 skipped cycles and an interval of amenorrhea (≥60 days)	Amen. x 12 mos	none	
<b>Endocrine:</b>	normal FSH		↑ FSH	↑ FSH		↑ FSH		

\*Stages most likely to be characterized by vasomotor symptoms.

Source: Stages of Reproductive Aging Workshop (STRAW), *Menopause* 2001.

misnomers sometimes used to describe perimenopause or the menopause transition. It is appropriate to say that one “reaches” menopause.

**Menopause transition.** According to STRAW, the term *menopause transition* (or *menopausal transition*) refers to the span of time when menstrual cycle and endocrine changes occur, and is divided into stage –2 (early) through stage –1 (late). The menopause transition begins with variation in the length of the menstrual cycle caused by a rise in levels of monotropic follicle-stimulating hormone (FSH) and ends with the FMP (which is recognized only after 12 consecutive months of amenorrhea). Women experiencing induced menopause (see below) do not experience this menopause transition.

**Perimenopause.** The term *perimenopause* is somewhat confusing. According to STRAW, perimenopause is defined as about or around menopause, beginning with stage –2 (early transition) and ending 12 months *after* the FMP (not *with* the FMP). NAMS prefers to use the term interchangeably with *menopause transition*, although there is a difference in the STRAW system. STRAW suggests that the term be used only with patients or in the lay press; NAMS uses the term for all audiences.

**Premenopause.** The term *premenopause* is used ambiguously. The literal meaning of the word implies the whole time preceding menopause, that is, the time before the FMP. CAMS recommends that this term encompass the entire *reproductive* period up to the FMP. STRAW does not use this term, but prefers classifying the reproductive stage as early, peak, and late (with “late” being the time when levels of FSH increase). In recent years, NAMS has used the term “premenopause” to refer to the time from menarche to the beginning of perimenopause. However, it is not appropriate to consider a young teenager “premenopausal.” To obviate confusion, NAMS concurs with the recommendation of CAMS to abandon the term “premenopause.” NAMS prefers the term recommended by STRAW—*menopause transition*.

**Postmenopause.** The term *postmenopause* refers to any span of time dating from the FMP, regardless of whether menopause was natural or induced. It is defined by STRAW as extending from stage +1 (early menopause) through stage +2 (late menopause).

Stage +1 is defined as the time span within 5 years after the FMP. During stage +1, ovarian hormone function is further dampened, resulting in a permanently low level. Stage +1 is also the time of accelerated bone loss. STRAW further divides stage +1 into segments *a* (the first 12 mo after the FMP) and *b* (the next 4 y). Stage +2 has a definite beginning (5 y after the FMP), but its duration is variable as it ends with death. STRAW concluded that further divisions may be warranted as more information is accumulated about the physiology of menopause.

**Induced menopause.** According to CAMS, the term *induced menopause* is defined as the cessation of menstruation that follows either surgical removal of both ovaries (bilateral oophorectomy, with or without hysterectomy) or iatrogenic ablation of ovarian function (eg, by chemotherapy or pelvic radiation therapy). Bilateral oophorectomy is the most common cause of induced menopause.

Fertility ends abruptly for women who experience surgically induced menopause (*surgical menopause*). With other types of induced menopause, fertility may end immediately or over several months. Depending upon the age of the woman, chemotherapy-induced ovarian failure may only be transient.

**Premature menopause.** According to CAMS, *premature menopause* should be defined as natural menopause that occurs at an age less than 2 SD below the mean estimated age for the reference population. In practice, CAMS states, the age of 40 years is frequently used as an arbitrary cutoff point below which menopause is said to be premature.

NAMS uses the term *premature menopause* to describe menopause reached at or under age 40, whether menopause is natural or induced.

**Early menopause.** NAMS uses this term to describe natural or induced menopause that occurs well before the average age of natural menopause (age 51 y)—at or under age 45. Early menopause encompasses premature menopause.

**Premature ovarian failure.** The term *premature ovarian failure* (POF) is used to describe ovarian insufficiency leading to amenorrhea that occurs in women younger than age 40. POF may be transient when caused by autoimmune disease or chemotherapy, but permanent loss of ovarian function is the usual outcome. Genetic abnormalities of the X chromosome are another important cause. POF reflects primary failure of the ovary with resultant high levels of luteinizing hormone (LH) and FSH. POF should not be confused with hypothalamic amenorrhea (HA). Overexercising, eating disorders, or high levels of stress can induce a reduction in ovarian hormone production, but as opposed to POF, the lack of ovarian function in HA reflects central suppression of the hypothalamic-pituitary-ovarian axis resulting in low levels of LH and FSH. Resumption of a normal lifestyle by women with HA is usually followed by resumption of normal menstrual cyclicity.

**Temporary menopause.** The term *temporary menopause* is used to describe a span of time when normal ovarian function is interrupted and temporary amenorrhea results. Since menopause is by definition the very last menses, NAMS does not use the term “temporary menopause” and recommends that the term be abandoned.

**Climacteric.** STRAW suggests that the term *climacteric* be used interchangeably with “perimenopause.” However,

CAMS defines climacteric as the age-related transition in women from the reproductive to the nonreproductive state. It is a process rather than a specific point in time. According to CAMS, the climacteric for women is sometimes, but not necessarily always, associated with symptomatology. When symptoms occur, they may be termed the “climacteric syndrome.”

STRAW has suggested that the term “climacteric” not be used in scientific papers. Global consensus on this terminology has not been achieved. NAMS does not use the term, but it is still widely used outside North America.

## Demographics

Exact figures on the number of postmenopausal women and the number reaching menopause each year are not known. To provide estimates, NAMS has extrapolated data from several sources to determine the number of postmenopausal women by age, by surgically induced menopause, and by premature menopause, and has presented them in Table 1.

**Table 1. Estimates of numbers of postmenopausal US women in 2000**

<i>Total number (prevalence)</i>	<i>(in millions)</i>
Age 51 and older*	39.944
Age 40 to 50	
(natural menopause)	3.123
Surgical menopause**	2.000
Premature natural menopause†	<u>0.504</u>
Total	45.571
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<i>Total reaching menopause during 2000</i>	
Age 51 and older	1.796
Surgical menopause†	0.228
Premature natural menopause	<u>NA</u>
Total	2.024
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<i>Total/day reaching menopause during 2000</i>	
	5,640

\* Includes women who may have experienced menopause earlier in life (induced or premature natural menopause).

\*\* From the National Hospital Discharge Survey, 2004; includes only women younger than age 50.

† Includes only women younger than age 40.

Source: US Census Bureau *Census 2000*.

**United States.** In 2000, there were an estimated 45.6 million postmenopausal women in the United States. About 39.9 million of them were older than age 51, the average age of natural menopause in the Western world. By the year 2020, the number of US women older than age 51 is expected to be more than 50 million.

NAMS estimated the number of postmenopausal women (see Table 1), extrapolating data from the 2000 US Census

and other resources. Details regarding the calculation of these estimates follow.

*Postmenopause by age.* Nearly 40 million US women are past the average age of natural menopause (51 y). Although the US Census Bureau year 2000 report does not provide the exact number of women over 51, it does report numbers for women aged 55 and older, who can all be assumed to be postmenopausal. An estimated 75% of women in the 50- to 55-year-old age category are assumed to be postmenopausal. These estimates include women who may have had induced or premature natural menopause earlier in life.

Among women aged 40 to 45 years, an estimated 5% have experienced natural menopause, based primarily on data from the Study of Women’s Health Across the Nation (SWAN). For naturally postmenopausal women in the next oldest category (45 to 55 years), a rough estimate is 25%.

For a 1-year estimate of the number of women experiencing natural menopause during 2002, the number of women aged 50 to 55 years was divided by 5 (approximately one fifth of the 50- to-55-year-old age group turned 51 in 2000).

*Surgical menopause.* The US hysterectomy surveillance (1994-1999) from the Centers for Disease Control provides estimated overall rates for hysterectomies by age plus percentages for those hysterectomies that included bilateral oophorectomy. Applying those rates to US Census Bureau data for premenopausal-aged women provides an estimate of the number of women who had undergone a hysterectomy with bilateral oophorectomy before age 50. No overall numbers are published for bilateral oophorectomies without hysterectomy. Given that bilateral oophorectomy without hysterectomy is relatively rare, a conservative estimate was added to round the number up to 2 million.

Data are inconclusive regarding the association of hysterectomy with ovarian failure occurring earlier than normal. Thus, numbers for that group are not included.

Annual numbers for surgical menopause come from the 2004 National Hospital Discharge Survey. Oophorectomy data for women aged 15 to 44 years plus 25% of women aged 45 to 64 years were combined to provide an estimate. The survey also provides data on hysterectomies, but it is not known whether those hysterectomies were with or without bilateral oophorectomy.

*Premature natural menopause.* Several studies, including SWAN, indicate that the percentage of US women experiencing premature natural menopause is approximately 1%. Applying this estimate to the number of women aged 15 to 40 years in the 2000 US census gave an estimate of the number of US women who experienced premature natural menopause. This is based on the total number of US cases; the annual figure is not known.

*Induced menopause from chemotherapy or pelvic radiation therapy.* There are no hard data from which to calculate estimates, so these women are not included.

**Canada.** Canadian statistics also demonstrate an increase in life expectancy for midlife women. In 1922, a 50-year-old woman lived until age 75 on average. Today, a woman the same age can expect to live until her mid-80s. Thus, Canadian women are living at least one third of their lives after menopause. By 2026, it is estimated that almost one quarter (22%) of the Canadian population will be comprised of women over the age of 50.

**Worldwide.** In 1998, there were more than 477 million postmenopausal women in the world and approximately 9% were expected to live to age 80. By 2025, the number of postmenopausal women is expected to rise to 1.1 billion. Life expectancy for women worldwide was 65 years in 1998 (79 y in more developed countries). This is expected to rise to 72 years worldwide by 2025 (82 y in developed countries).

## How to evaluate the medical literature

As new studies are published, the evidence base increases for understanding the risks and benefits of treatment options. A basic understanding of the types of studies and the meaning of the analyses helps healthcare providers evaluate the evidence and implications for clinical practice. Readers in search of more sophisticated discussions are urged to consult current clinical epidemiology texts.

**Types of studies.** Two major types of studies are *experimental* and *observational*. In experimental studies, interventions and conditions are strictly defined and controlled by the investigators. In observational studies, investigators observe outcomes in relation to variables of interest. They do not assign participants to an exposure of interest. The most common types of studies are listed here, ordered by the strength of evidence they provide.

*Experimental studies.* Types of experimental studies are randomized controlled trials (RCTs), crossover trials, and quasi-experimental studies.

- *Randomized controlled trials* are considered the strongest for therapeutic interventions. In RCTs, a group of participants with similar characteristics is identified (eg, low bone density). Each participant is then “randomly assigned” (neither the participants nor the investigator chooses) to an intervention group (or groups) or to a control group. Participants typically have an equal and unbiased (ie, random) chance of being assigned to each treatment under study. RCTs have the best chance of avoiding selection bias if the randomization is adequate. This is because known and unknown characteristics should be the same in each group. The baseline characteristics of the two groups should be presented and statistically compared in an

RCT’s final report. The Women’s Health Initiative is an example of an RCT.

RCTs are best suited to situations in which exposure to treatment is modifiable, a legitimate uncertainty exists regarding benefit and/or harm of treatment, and outcomes are reasonably common. However, inclusion and exclusion criteria may limit the extrapolation of the results to other groups (ie, whether the results can be generalized).

The “power” of a trial is the likelihood that it will determine the effect of the intervention. The number of participants is determined when the trial is designed based on the likelihood of the measured outcome events and the anticipated magnitude of the intervention’s effect. If events do not occur as often as predicted, the trial may not have adequate power to determine the effect of the intervention. The Methods section of the published trial results will describe how the investigator calculated the number of participants required and will quantify the range of effect the study can detect (eg, the study was powered to detect more than a 20% reduction in heart attacks). Publication bias favors small trials with positive outcomes. An international registry of clinical trials requires submission of the planned trial so that a full accounting of the status of trials that are not completed or are completed regardless of their outcomes can be assessed.

Depending on the intervention, participants and investigators may be purposefully blinded or masked (ie, they do not know which treatment a participant is receiving). This helps reduce some forms of bias and the effects of the participant’s or investigator’s expectations of intervention benefit.

Classically, RCTs are used to assess for *efficacy* of the treatment in an ideal controlled setting. More often now, an RCT will assess *effectiveness* (not efficacy) by studying the intervention under more usual circumstances. This is because a study for efficacy may not reflect its actual effectiveness in a real-world, clinical practice setting. Both these types of RCTs often use a relatively narrowly defined patient population. Even though an RCT is quite “internally valid” (ie, the study was done well), it may not be accurate to extrapolate (generalize) the results from one RCT to another patient population that was not studied in the trial.

Other important issues when evaluating the results of an RCT include checking to see whether all participants who started the trial were accounted for at trial conclusion and whether the groups were treated equally aside from the experimental intervention.

- *Crossover trials* allow participants to serve as their own controls. Participants are randomly assigned to one treatment arm and later switched to the other treatment

arm. This “crossover” study methodology has often been used in trials to assess the efficacy of medications. The design is difficult to do well because of its potential for residual effects between interventions. Often there will be a washout period (time during which no intervention is given) between interventions.

- *Quasi-experimental studies* are of two general varieties. In one, two interventions are simultaneously compared in two groups of participants, but interventions are not randomized for any given participant (eg, two hospitals comparing two types of wound closure for the same type of surgery).

Another common quasi-experimental study is when participants serve as their own controls and the investigator controls the intervention. The intervention is neither randomized nor is there a control population to which the response can be compared. After baseline evaluation, the intervention is given and the participants are reevaluated to observe any changes in characteristics because of the intervention.

*Observational studies.* Types of observational studies include purely *analytic* (or *descriptive*) studies. Analytic studies (including cohort studies, case-control studies, and cross-sectional studies) have a nonrandomized control group (eg, women who did not use HT for any number of reasons would be compared with women who elected to use HT). What is sampled first—risk factor, outcome, or both risk factor and outcome simultaneously—determines which analytic study design is being used. Case reports and case series are not analytic because they do not have control comparisons.

- *Cohort studies* (or *longitudinal studies*) begin with a defined group of participants (eg, individuals of a certain age or those who work in a certain industry) called the “cohort.” These studies sample individuals from the general population and determine if they have risk factors of interest (eg, HT users vs nonusers). This cohort of individuals is then followed over time to study a variety of outcomes. Data are collected in a similar manner on all participants from the beginning of the study (the baseline) and frequently at set intervals during follow-up. The Nurses’ Health Study is one of the best-known cohort studies.

These studies provide a clearer temporal sequence of exposures and/or outcomes, are well suited for common exposures, and can study multiple exposures and/or outcomes. However, they can be time-consuming and expensive, they have the potential for many forms of bias, and participants may be lost during follow-up. When too many patients are lost, the validity of the study is compromised.

Cohort studies may follow relevant events as they occur over time (prospective), but they may also be performed in an historical or a concurrent (cross-sectional) manner. Evidence from prospective cohort studies is considered stronger than the other forms of analytic studies because data on exposures are collected before the outcomes occur.

The term *retrospective* is sometimes used when referring to an historical cohort study, and it can be confusing. If the data are easily accessible, the researcher can retrospectively evaluate a cohort that was followed in time, but the time was in the past moving forward (historical cohort), not progressing from current time onwards (concurrent cohort). In the Nurses’ Health Study and the Framingham Study, information was gleaned in a concurrent and retrospective fashion (where a historical cohort was evaluated). All participants in each of these circumstances were followed longitudinally forward in some time frame.

- *Case-control studies* begin with an outcome or disease of interest (eg, myocardial infarction [MI], breast cancer) and then compare the characteristics or risk factors of individuals with the outcome (cases) to controls who do not have the outcome or disease of interest. Case-control studies are prone to many more forms of bias. A frequent one is “recall bias” (ie, participants cannot remember accurately).

Matching participants for specific characteristics and defining strict eligibility criteria lessens, but cannot eliminate, the possibility that the results are “confounded.” For example, women who use HT are known to smoke less and lead generally healthier lifestyles. HT users have less cardiovascular disease primarily because of better lifestyle habits rather than any beneficial effect from HT use. Smoking or other lifestyle patterns can confound the results when observational studies analyze HT use and health outcomes. Matching cases and controls for smoking status helps reduce this confounding.

Despite these limitations, case-control studies have many advantages. Because they begin with an outcome of interest, they can be performed efficiently and at less cost than cohort studies. They are important in situations in which it would be unethical to assign individuals to an exposure (eg, chemotherapy) or when an outcome is rare (eg, X-chromosome abnormalities associated with POF).

- *Cross-sectional studies* are snapshots in time. Here, cases and controls are evaluated at the same time for both risk factors or characteristics and outcomes of interest. Cross-sectional studies are very useful for determining prevalence, for planning for healthcare needs, and for generating hypotheses.

- *Case reports* and *case series* describe the experience of a single patient or series of patients. Such reports are useful in bringing new diseases or phenomena to the attention of the clinical and scientific community and for generating new hypotheses. However, lacking a control group, case reports or series without further study are only suggestive.

Many of these basic designs can be modified or combined, and many hybrid studies exist. An example is a case-control study within a cohort; this is a very useful study design and can provide many advantages, including cost.

**Analyses.** The bottom line in evaluating a study is, “What are the results?” The results of cohort studies and clinical trials are most frequently presented as a relative risk (RR)—the likely level of greater risk (eg, for HT users compared to nonusers). The RR can be determined because these study designs follow participants longitudinally and risk (which is time-dependent) can be determined in each comparison group. Definitions of key terms used in analyzing study results are as follows:

*Rate/risk.* The term *rate* is the number of events per number of individuals per time interval (eg, 44 per 10,000 per year). Knowing the exact number of events over time is very useful, as this determines the *risk*.

The Council for International Organizations of Medical Sciences Task Force has provided the following nomenclature to guide the interpretation of risks:

- Rare = less than or equal to 10/10,000 per year
- Very rare = less than or equal to 1/10,000 per year

Rare outcomes would not be of such great concern to an individual woman making a decision about treatment. However, it is important to recognize that common exposures that produce rare outcomes can still have profound public health impact.

*Relative risk (RR).* RR is a ratio—the rate of disease or the outcome of interest in a group exposed to a potential risk factor or treatment, or having a characteristic of interest, divided by the rate of disease or interest in an unexposed group (ie, those without the risk factor, treatment, or characteristic of interest). The RR should be used only for prospective studies.

Rate is used as above in both the numerator and the denominator. These are the numbers of events, per numbers of individuals, per time interval (eg, 50/100,000/year). For example, if the annual rate of MI in women who smoke is 220 per 100,000, and the annual rate in women who do not smoke is 110 per 100,000, the RR associated with smoking is:

$$RR = \frac{220}{100,000/\text{year}} \div \frac{110}{100,000/\text{year}} = 2.00$$

This means that compared with nonsmoking women, the risk of MI for a smoking woman is twice that of a nonsmoking woman in the study.

An RR *less than 1.0* suggests lower risk. For example, an RR of 0.50 means there is a 50% less chance (or risk) of the outcome studied in those with versus those without the risk factor of interest. An RR of 0.3 means a 70% less relative risk.

An RR *greater than 1.0* suggests that the factor increases risk. For example, an RR of 1.2 means there is a 20% increase in risk in the group with the factor versus the group without the risk factor. An RR of 2.0 means double the risk.

*Odds ratio (OR).* The OR is an estimate used in any of the analytic studies. It best approximates the RR when the outcome is rare.

*Confidence interval (CI).* The CI, usually cited with the RR or the OR, indicates with a certain degree of assurance the range within which lies the true magnitude of the measured effect. The CI has two components—the point estimate and a range (eg, RR, 1.20; 95% CI, 1.09-1.32). The point estimate (the RR or OR number) is the best mathematical estimate from the data. Understanding the upper and lower limits of the range is often clinically useful. If the CI is “wide,” the reader’s confidence in the validity of the RR would be less than if the CI is “narrow” (ie, closer to the value of the RR).

Often, a 95% CI is used. A 95% CI gives the range of values that have a 95% probability of containing the true RR or OR. When a 95% CI does not contain the number 1.0 (eg, 0.40-0.80 or 1.12-1.37), the measured RR or OR is significant by at least  $P < 0.05$ . The CI is more clinically useful than the  $P$  value (see below) because the CI helps the reader to understand the best estimate of the effect and it also provides the mathematical estimated limits, which are useful in determining the best-case and worse-case scenarios.

*P value.* This term is the probability of obtaining the observed RR or OR by chance alone. A  $P$  value of .01 means that there is a 1% mathematical probability that the observed difference between two groups occurred by chance. By convention,  $P$  is generally deemed significant if below .05. This means that if 20 outcomes are evaluated in a single study, one of these outcomes is likely to show a positive result just due to chance alone ( $P = .05$ , or 1/20). By the time  $P = .001$ , the likelihood is only 1/1,000 that the results occurred by chance—in other words, the finding is more likely to be real.

It is important to remember that a study can be *statistically* significant and not *clinically* significant. However, if it is not statistically significant, it cannot reach clinical significance and the result could be “clinically nonsignificant” or “inconclusive.” An example is when the study is underpowered.

**Attributable risk/absolute risk (AR).** The impact of RR on both a population and an individual basis depends on “incidence” (ie, the number of new cases). This can be quantified by the AR, which is the difference between the incidence rates in the exposed and unexposed groups—in other words, the “risk difference.” The AR quantifies the effect of exposure, providing a measure of its public health impact. For example, for the calculation presented earlier about the risk of MI in smoking women, the AR is:

$$AR = \frac{220}{100,000/\text{year}} - \frac{110}{100,000/\text{year}} = \frac{110}{100,000/\text{year}}$$

This means that for every 100,000 women who smoke, there would be 110 additional cases of MIs per year.

Often, AR is more clinically useful than RR in explaining risk to patients.

**Number needed to treat (NNT).** To communicate this risk difference to patients, the NNT can be useful. The NNT is merely the reciprocal of the AR (ie, 1 divided by the AR). For example, in a 1-year study, if the rate of an outcome was 20 per 1,000 in an untreated group, and 10 per 1,000 in a treated group, the NNT is:

$$NNT = \frac{1}{(20/1,000) - (10/1,000)} = \frac{1}{(10/1,000)} = \frac{1}{0.01} = 100$$

This means that for every 100 people treated, there would be 1 less negative outcome over the year.

**Meta-analysis.** This term describes an analytic technique used to pool the results of clinical trials. Often, a meta-analysis is performed on a group of studies that are too small to have statistical significance by themselves but that may show significance when pooled. Specific criteria (eg, eligibility criteria of participants, data completeness) are established to determine which studies will be included in the analysis. Since any biases present in the contributing studies will be present in the meta-analysis, the outcome of a meta-analysis is only as good as the studies included.

In general, meta-analyses are difficult to perform. They are best performed based on the original data obtained from each investigator from each individual study. International guidelines provide checklists to understand the quality of a meta-analysis of clinical trials (CONSORT guidelines) and observational studies (MOOSE guidelines).

## Suggested reading

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