JOURNAL OF WOMEN'S HEALTH
Volume 14, Number 9, 2005

Special Report

Biomedical Research on Health and Performance of Military Women: Accomplishments of the Defense Women's Health Research Program (DWHRP)

KARL E. FRIEDL, Ph.D.

ABSTRACT

In 1994, Congress provided $40M for biomedical research on issues of importance for military women. This supported 104 intramural and 30 extramural studies and launched an era of research to narrow the knowledge gap on protection and enhancement of health and performance of military women. Projects addressed issues specific to female physiology (e.g., gynecological health in the field, maternal malaria), problems with higher prevalence for women (e.g., marginal iron deficiency, stress fracture), and issues of drug and materiel safety that had only been extrapolated from studies of men (e.g., chemical agent prophylaxis, fatigue countermeasures). Several important assumptions about female physiology and occupational risks were found to be astoundingly wrong. Hormonal changes through the menstrual cycle were less important to acute health risks and performance than predicted, exercise did not increase risk for amenorrhea and consequent bone mineral loss, and women tolerated G-forces and could be as safe as men in the cockpit if their equipment was designed for normal size and strength ranges. Data on personal readiness issues, such as body fat, physical fitness, nutrition, and postpartum return to duty, allowed reconsideration of standards that were gender appropriate and not simply disconnected adjustments to existing male standards. Other discoveries directly benefited men as well as women, including development of medical surveillance databases, identification of task strength demands jeopardizing safety and performance, and greater understanding of the effects of psychosocial stress on health and performance. This surge of research has translated into advances for the welfare of servicewomen and the readiness of the entire force; relevant gender issues are now routine considerations for researchers and equipment developers, and some key remaining research gaps of special importance to military women continue to be investigated.

U.S. Army Research Institute of Environmental Medicine, Natick, Massachusetts.

The opinions and assertions in this paper are those of the author and do not necessarily reflect the official views of the Department of the Army or the Department of Defense.

INTRODUCTION

At the semiannual meeting of the Defense Advisory Committee on Women in the Services (DACOWITS) in 1999, one of the keynote speakers stated that it was time to declare success on the integration of women in the military and move on to team building and other issues. This was only a few years after Congress had provided the first of two $40M special appropriations for biomedical research to bring protection of the health and performance of military women on a par with men, after more than a century of research based solely on males. This paper takes stock of the accomplishments of the entire 1994 research program investment. Most of the key findings have now been published, and many of the ensuing recommendations and follow-on research efforts have been implemented.

The 1994 appropriation was originally intended to build a military women's research center in Colorado. The announced closure of Fitzsimmons Army Medical Center in Aurora, Colorado, altered those plans, and the final congressional conference language allowed for funding that would accelerate and augment research on military women's health and performance issues within existing research infrastructure. These issues were becoming more important as more jobs were opening to women. In 1994, the risk rule for gender-based job assignments was rescinded and replaced by a policy that only excluded women from units with direct ground combat missions and a few other specialized circumstances. With more women coming into the military, there was also a growing awareness of gender-unique problems, such as high injury rates; renewed questions about women's psychological fitness as fighters; assumptions about the fragility of the female reproductive system; and new concerns about occupational and environmental exposure hazards that might affect pregnant servicewomen or harm their fetuses. Much mystery and overstated significance were attributed to the effects of menstrual cycles, perpetuated by the general exclusion of fertile women from research studies, in part because of large variability assumed to be introduced by ovarian hormone fluctuations. This conundrum was reversed by the 1993 NIH Revitalization Act that demanded inclusion of women of childbearing age in each research project, and human use committees stopped accepting excuses about the inconvenience of assumed menstrual cycle effects. The large knowledge gaps in female physiology also led to challenges of nearly every policy that could be construed as providing preferential treatment to servicewomen, calling for additional information to defend or refute policies and standards. This confluence of increasing need, awareness, and opportunity to address health issues of military women led to a decade of fruitful research discovery and significant advances in several areas, although there were also significant failures.

The Defense Women's Health Research Program (DWHRP) was organized and directed through the Military Operational Medicine Research Program (MOMRP) at the U.S. Army Medical Research and Materiel Command (Fort Detrick, Maryland). The funds were divided, with half distributed for immediate execution to 104 intramural projects at Army, Navy, and Air Force laboratories and the other half dedicated to 30 competitive extramural projects that would address a list of 10 key research gaps (Table 1). These were selected from 232 intramural and 193 extramural proposal submissions. Less than 1% of the funding went to administrative costs. These were exclusively the costs of independent peer review, with the remaining program costs (i.e., contracting, human and animal use review and oversight, fiscal management, science and grant management and oversight, and report and information management) subsidized by the existing Army research management infrastructure. Even a mandatory deduction to support the Small Business Innovative Research (SBIR) program was recouped with a DWHRP topic on development of a semiquantitative test for progesterone and estrogen metabolites to identify menstrual cycle stages. A summary report with details of the individual projects and program management is available on request.

OVERALL PROGRAM ASSESSMENT

Topics and projects

Issues specifically targeted by the DWHRP and the relative success in addressing these topics with the proposals received are summarized in Table 1. These topics and priorities were based on information accumulated within the MOMRP, representing an integration of congressional,

Table 1. Research Priorities Report Card

Advertised issue or problem	*DWHRP94 project transitions*	*Significant DoD follow-on research*
1. Strategies to overcome strength limitations	*Successful* Provided a scientific basis for new physical training programs in development on the basis of female strength trainability	Defense Technology Objective on effective physical training without increasing injury
2. Incidence and causes of injury and illness	*Successful* Provided a foundation for current DoD electronic medical surveillance systems and tools for injury and illness monitoring and risk mitigation	Establishment of Center for Deployment Health Research and Millenium Cohort study
3. Assessment of the stress of military life related to attitudes and social roles	*Limited success* Focused new attention on the high prevalence of sexual harassment and violence, its importance in health, and the key role of leadership	UCSF-USARIEM study on health risk communication, including sexual harassment and violence prevention
4. Protection against reproductive and teratological material hazards	*Limited success* Provided alternate treatments for some key endemic diseases faced in deployments	DoD Birth Defects Registry and pediatric cancers research
5. Reduction in stress fracture incidence	*Limited success* Reduced emphasis on techniques to assess recruit bone density, moving to bone geometry considerations in continuing research	Bone Health and Military Medical Readiness Research Program
6. Improvement of reproductive and gynecological healthcare	*Limited success* Developed an effective training program for female Marine recruits to reduce STD and UIP prevalence	
7. Prevalence and consequences of mineral deficiencies (e.g., iron, zinc)	*Unsuccessful* (Some studies completed but inconclusive)	New USARIEM research initiative on iron and zinc nutrient requirements
8. Extending performance limits in extreme environments and continuous operations	*Successful* Put to rest gender issues about differential health and performance in extreme natural and occupational environments, and safety of drug countermeasures not previously tested in women	
9. Military equipment and material design considerations	*Limited success* Identified need for equipment and task redesign solutions for materiel developers	Army light-wheeled vehicle mechanic strength-injury study
10. Clinical health issues	*Limited success* Identified challenges to smoking cessation programs for military women; seeded research on more effective antifungal drugs, migraine drugs, and treatments for PMS and breast pain	Defense Technology Objective on health behavior interventions

DACOWITS, and identified service problems. Although some very important advances were made on these priorities, several topic areas were simply too hard to address with existing approaches. Instead, some of these efforts ended up refining test methods through feasibility studies (e.g., reproductive hazards evaluation; psychosocial assessments, bioavailable zinc measurement).

Investigation in these areas appears to have been simply too challenging, and these continue as important knowledge gaps, but the pilot studies are important to discovery of better approaches to solving the health and performance questions.

Most projects were completed, but success varied across organizations, as measured by a published report containing a valid and thorough analysis of the data. Every project resulted in a final report, but of the intramural projects, only half have resulted in open literature publications 10 years later. Unfortunately, this means that for the other half of the projects, most researchers, policymakers, and others who may have benefited from the results may never know the study was conducted, nor will there be any assurance of a proper analysis and some level of critical review. Extramural projects were more consistently successful; those that fell short of expectations were the ones that relied in some significant way on a federal agency partner (not necessarily Department of Defense [DoD]). This highlighted the marked contrast between the scientific culture in academia (focused on discovery) and that of many government laboratories (reacting to near-term problems), where academics were more likely than federal investigators to thoroughly analyze and publish their findings. The projects that led to the greatest benefit for military women were the ones where definitive results could be translated into policy, standards, materiel design specifications, and preventive medicine guidance. Thus, publication was a necessary but not sufficient measure of success.

Publications

As of the date of this paper, there were 245 publications from the 1994 DWHRP projects. This translates into at least one key publication per $200,000 invested. Some prolific investigators produced numerous papers from their projects. The true costs are higher, as many of the intramural projects were subsidized by existing infrastructure not captured in indirect costs. Extensive commingling of DWHRP and core program funds was encouraged, as many of these projects permitted augmentation of ongoing mission research with the inclusion of female subjects. The median time to publication of results, starting

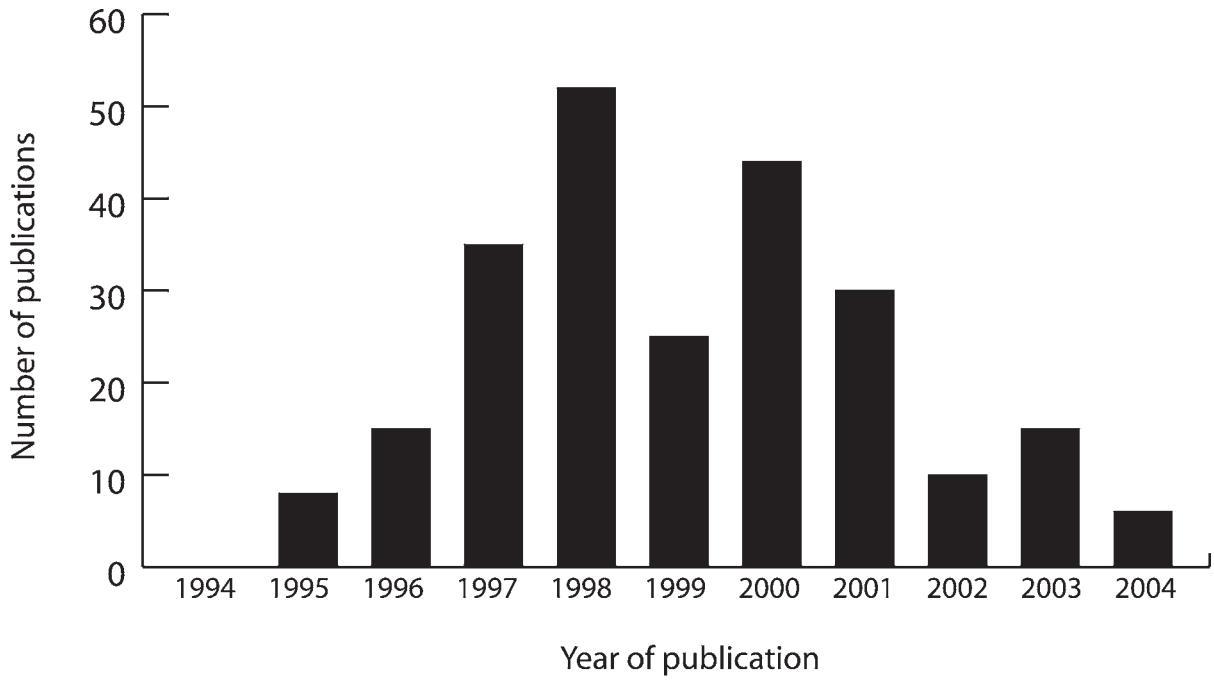

FIG. 1. Annual frequency of publications supported by the Defense Women's Health Research Program. Funding regulations limited intramural projects to a maximum period of performance of 2 years and extramural projects to 7 years; however, extramural contracts and additional sources of funding extended the life of some projects. Publications peaked at 3–5 years after project initiation, but results of some important studies have only recently been reported.

from the time of the project awards, was approximately 5 years, but some important studies have only recently concluded (Fig. 1).

The most highly cited papers from the program are listed in Table 2. This is an important measure of the relative impact of a published report, but citation frequency is also heavily influenced by journal visibility, topicality of the subject, and the type of finding (e.g., a new method). Thus, many publications from this program also represent important findings but will never achieve popular citation status.

All references cited in this paper and listed in the bibliography were supported through the DWHRP. Unpublished final reports (which are retrievable through the National Technical Information Service) are cited only in the absence of a published paper.

Peer review and selection

Peer review evaluations of the extramural proposals did not reliably predict success as measured by important findings or publications. Within the range of projects considered for funding, several of those with the lowest scores that were actually funded produced very important findings. In each of these cases, the principal investigators were primarily faulted for their relative inexperience but were funded anyway on the basis of the proposed science. The converse was also true, where several of the top-rated proposals failed either because of the loss of key investigators or a flawed central premise that was not identified by the reviewers. These observations suggest two truisms about conventional and competent peer review panels: they are risk averse, and they cannot be expected to anticipate certain sources of failure (e.g., unexpected deaths of two principal investigators). On the other hand, three projects scored outside of the normal fundable range but were funded for other reasons; each of these projects failed to produce anything of value, confirming the value of proper peer review in rejecting poor proposals. Funding to intramural projects was provided on the basis of service priorities; scientific review and human and laboratory animal use reviews were conducted according to individual service and laboratory policies. All reasonable proposals from intramural laboratories and all identified service priorities were supported. This saturation of the available intra-

Table 2. Most Frequently Cited Publications

1. [a]Fried M, Duffy PE. Adherence of *Plasmodium falciparum* to chondroitin sulfate A in the human placenta. *Science* 1996;272:1502.
2. [a]Gaydos CA, Howell MR, Pare B, et al. *Chlamydia trachomatis* infections in female military recruits. *New England Journal of Medicine* 1998;339:739.
3. Young SA, Hurt PH, Benedek DM, Howard RS. Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: A randomized, double-blind, placebo-controlled crossover trial. *Journal of Clinical Psychology* 1998;59:76.
4. [a]Carter CS. Neuroendocrine perspectives on social attachment and love. *Psychoneuroendocrinology* 1998;23:779.
5. [a]Braun B, Mawson JT, Muza SR, et al. Women at altitude: Carbohydrate utilization during exercise at 4,300 m. *Journal of Applied Physiology* 2000;88:246.
6. Fulco CS, Rock PB, Muza SR, et al. Slower fatigue and faster recovery of the adductor pollicis muscle in women matched for strength with men. *Acta Physiologica Scandanavica* 1999;167:233–9.
7. Andersen SL, Oloo AJ, Gordon DM, et al. Successful double-blinded, randomized, placebo-controlled field trial of azithromycin and doxycycline as prophylaxis for malaria in western Kenya. *Clinical Infectious Diseases* 1998;26:146.

High citation rates expected (projects only recently reported)

Boyer CB, Shafer MA, Shaffer RA, et al. Evaluation of a cognitive-behavioral, group, randomized controlled intervention trial to prevent sexually transmitted infections and unintended pregnancies in young women. *Preventive Medicine* 2005;40:420.

Butte NF, Wong WW, Treuth MS, Ellis KJ, Smith EO. Energy requirements during pregnancy based on total energy expenditure and energy deposition. *American Journal of Clinical Nutrition* 2004;79:1078.

[b]Loucks AB, Thuma JR. Luteinizing hormone pulsatility is disrupted at a threshold of energy availability in regularly menstruating women. *Journal of Clinical Endocrinology and Metabolism* 2003;88:297.

[a]Most cited reference from projects with more than one highly cited publication.
[b]"Best paper of 2003" for *Journal of Clinical Endocrinology and Metabolism*.

mural resources means that any additional funds could only have been used wisely by supporting more extramural projects.

Accomplishments

The rest of this paper summarizes key projects and accomplishments of the program. This discussion is organized around eight categories of problems addressed by the DWHRP. Table 3 summarizes 20 top accomplishments of the program within these eight categories. Also summarized are known transitions of the findings to policy, materiel, and preventive medicine applications, as well as efforts to follow up on important findings in remaining gap areas of research. Other metrics of success (not presented in this paper) are the new investigators who were attracted to this type of research and mentored through these projects, other grant support that investigators were able to obtain on the basis of findings from these projects, and patent and other intellectual property developed from these studies.

PHYSICAL STRENGTH DEMANDS AND STANDARDS

Strength standards

In standard tests of upper body strength, only the strongest women reach into the lower end of the male distribution of strength capabilities. This has been regarded as a barrier to the full integration of women into military jobs. Specific occupational strength standards were extensively investigated in the early 1980s, and all services attempted unsuccessfully to implement strength testing of recruits for job classification. Sara Lister, an assistant secretary of the Army, forced a more careful study design in DWHRP performance research to ensure that studies were not constructed around foregone conclusions that physical strength was the central determinant of job success. Although some tasks, such as litter bearing and marching with load carriage equipment, required specific strength capabilities,[1,2] individual strength tests remained poor predictors of success in any military specialty, primarily because physical tasks can usually be accomplished through a variety of strategies and commonly involve team efforts with multiple roles.

Task and equipment design

Isolated tasks that require great strength often represent a human engineering design shortfall and present an injury risk to anyone performing the task, regardless of gender. The preferred solution is equipment or task redesign rather than selection or unusual adaptation of the users. DWHRP studies uncovered several such problems. For example, manual foot and hand controls in some Navy aircraft could not be activated for critical emergency tasks by most women.[3] This led to a more comprehensive Navy program in task and equipment analysis and redesign. New data for helmet design criteria were produced from Air Force studies of female neck strength tolerance.[4] This contributes to current triservice efforts to develop a valid neck model for design of head-supported loads. Lifting tasks were examined in a detailed series of biomechanical studies that expanded existing spine models for manual material handling tasks. These studies demonstrated that women are not simply scaled-down versions of men; women had lower spine compression loads during lifting but also had lower spine tolerances.[5,6] However, the net effect has not translated into higher hospitalization rates for acute back problems for women.[7,8] Light-wheeled vehicle mechanics represent an Army occupational specialty with the highest prevalence of musculoskeletal injuries.[7] A current study used this finding to test the general hypothesis that strength deficiencies are associated with injury risk in this common Army specialty, comparing injuries to mismatches between strength of individuals and critical task demands. The presence or absence of a compelling relationship between physical strength and either job performance or injury risk in this study will help put this issue to rest or reopen the door to further examination of occupational strength requirements and task design. Findings from all these studies can be used to improve designs of helmets and personal equipment, occupational tasks, and vehicles and aircraft better matched to typical human capabilities and tolerances.

Women were handicapped in several other ways by equipment originally designed with only men in mind. In a 10-km road march with loads up to 36 kg, women reported more problems with the shoulder straps over narrower shoulders, fit of the pistol belts over smaller waists and chafing on the hips, and the fit and stability of the

TABLE 3. TWENTY SIGNIFICANT ACCOMPLISHMENTS OF THE 1994 DEFENSE WOMEN'S HEALTH RESEARCH PROGRAM

Determined trainability of female strength capacity, providing data for development of effective science-based physical training programs to enhance job safety and performance
Identified design features of military equipment that hamper safety and performance, highlighting opportunities and needs for equipment and task redesign
Characterized bone geometry differences associated with stress fractures that help explain injury susceptibility to help identify individuals for future intervention programs
Demonstrated the feasibility of a medical epidemiological database system, contributing to the establishment of the Defense Medical Epidemiological Database (DMED) and the formation of DoD epidemiological research surveillance centers.
Demonstrated the importance of energy balance in normal ovarian function and on bone metabolism, debunking the female athlete triad hypothesis that suggested health risks to normal women from intensive exercise
Characterized appropriate gestational weight gain and energy requirements for healthy women, providing data to guide return to duty postpartum standards
Resolved mismatches for women in medical, fitness, and nutrition military regulations to more effectively promote readiness and not impair health (e.g., DODI 1308.3)
Defined high rates of *Chlamydia* infection in recruits, and compared cost-effectiveness of management protocols for preventive medicine programs that will reduce pregnancy complications and infertility
Demonstrated effectiveness of a health risk training program for STD/UIP prevention, establishing a basis for further health risk communication research
Discovered the pathophysiology of maternal malaria, opening the door to development of a vaccine that may be universally effective against maternal malaria
Demonstrated effectiveness of azithromycin as a pregnancy-safer prophylaxis/treatment for falciparum malaria and scrub typhus, providing alternative treatments with existing approved antibiotics
Developed a novel computing approach to provide up-to-date research information in a decision-assist tool, demonstrated with the DoD Breast Cancer Decision Guide
Identified special challenges to help military women quit smoking, including a selective effect of military service in attracting hardcore smokers, which will guide follow-on research efforts
Supported the first analysis of health behavior trends of military women using the periodic DoD survey, identifying gender differences in health risk behaviors and their relationship to stress coping strategies
Identified adverse effects on individual health and unit readiness produced by sexual harassment and sexual violence
Determined the prevalence of illnesses in female Gulf War veterans, including exploration of multiple chemical sensitivities and related chronic multisymptom illness symptoms
Discovered that hormonal changes through the menstrual cycle play a smaller role than previously assumed in performance and environmental injury susceptibility
Identified problems of voluntary dehydration in military women and provided solutions, including materiel solutions, to facilitate urination in special environments and training solutions to improve urine retention
Characterized the physiology of women at altitude, demonstrating neither significant advantages nor disadvantages of ovarian hormones
Discovered that assumptions about increased risk for women from decompression sickness and G-force were wrong

rucksack.[2] Even though women were disadvantaged by their own equipment and finished marches 21% slower than the men, the average female march rates were still faster than the field manual predictions for soldiers. Newer research on the biomechanics of load carriage equipment is contributing to better designs, and backpacks have been constructed to accommodate female dimensions. Load carriage issues will be further mitigated with new concepts that take much of the weight off the soldier of the future.

Physical training

Strength training had been well studied in men, but masculinizing hormones play an important role in these training responses, leaving open the question of how much strength could be increased in normal women. In DWHRP training studies, women significantly improved their strength capabilities, demonstrated marked physiological changes such as body composition, and improved their ability to meet testing thresholds for simple manual material handling tasks. A 14-week physical training program that emphasized progressive resistance and running training for an hour per day produced modest improvements in job-specific material handling tasks in female soldiers.[9] A more intensive 24-week training program with supervised aerobic and resistance training for up to 90 minutes per day substantially increased the proportion of women who qualified for "very heavy" Army jobs, although these training benefits were counterbalanced by relatively high injury rates, even with great care to minimize this risk.[10–12] In the most ambitious study, five different 24-week training programs were compared, demonstrating the importance of specific training components, such as low repetition resistance exercise and explosive exercises, to improving specific military task performance such as the box lift and load carriage[13–15] (Fig. 2). By the end of the training, resistance-trained women could run with a 75-pound pack as fast as a comparison group of 100 men. In each of these three training studies, women gained lean mass and lost fat mass,[9,12,16] and the studies clearly demonstrated the ability of normal women to respond to resistance training with upper body muscle hypertrophy, yet none of the initial concerns about creating "female Rambos" with a big muscle look were realized.[16] These study results contribute to current efforts to revamp physical training and testing as part of a new defense research initiative to improve physical training while reducing injury rates.

Military fitness tests

Military fitness tests, required at least annually in all services, are gender appropriate (i.e., they are scaled to recognized physiological differences) rather than gender neutral, as these generalized tests are intended to motivate fitness training and are not linked to any threshold of job performance. Most of the services set standards relative to current performance within age as well as gender groups; these are based on occasional surveys of fitness test performances. Sit-up standards have finally converged for men and women, and run times have drawn closer over time. However, upper body strength differences make the strength testing component (e.g., push-ups or pull-ups) a gender issue. Push-up performance was studied in women who could barely pass the event compared with women who achieved maximum scores. Firing patterns of 15 muscles in the upper body revealed that women who excelled had effective neuromuscular control demonstrated in a smoother pattern of motion, and marginal performers were at risk for specific types of injuries, such as to the rotator cuff.[17] Training recommendations were developed for women having difficulty with the push-up. A separate study examined modes of failure in push-up performance by selectively fatiguing seven different muscle groups, followed by push-up testing. This study indicated that the pectoral and triceps muscles were critical targets for any selective training program to improve push-up performance in women.[18]

STRESS FRACTURES IN INITIAL ENTRY TRAINING

Women have twice the injury rates of men, including serious time-loss injuries, and half of female recruits sustain musculoskeletal injury in initial entry training in all military services.[19–21] Some of the higher injury rates reported for female military trainees are explained by more reliable reporting by women,[22] but women are clearly at higher risk for some injuries, such as stress fracture. Stress fracture rates ranged from 5% to 15% in women compared with 1% to 3% in

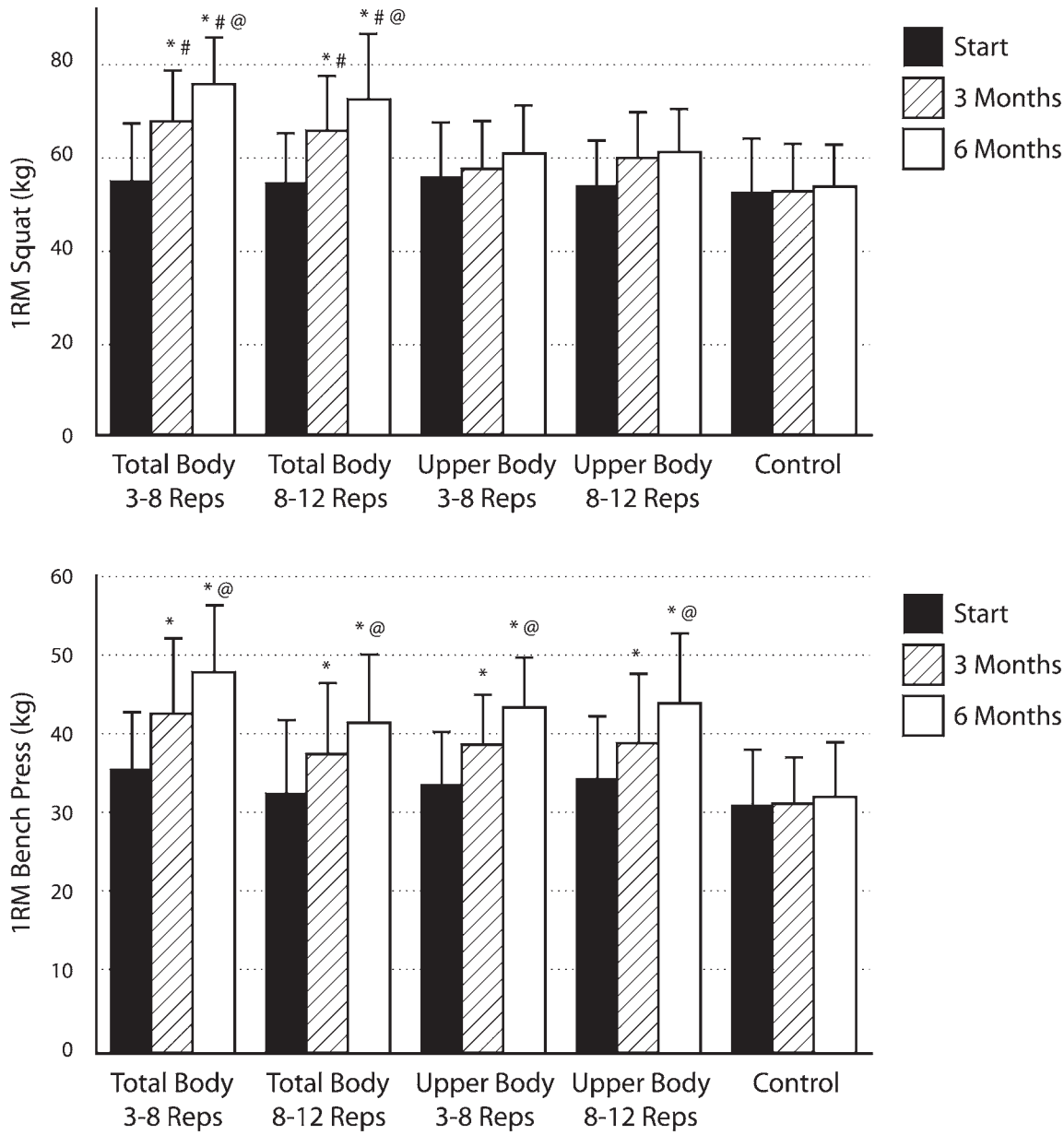

FIG. 2. Comparison of strength performance outcomes for women participating in four different 6-month physical training programs and in a control group with no training (reproduced with permission from ref, 14). The greatest benefits to single maximal repetition (1 RM) of the bench press and squat exercises occurred with total body training programs with low (3–8 RM) or high (8–12 RM) repetition routines compared with training programs focused only on the upper body. Such training studies provide a scientific basis for programs to enhance strength performance of women. Significant changes at $p < 0.05$ are indicated for comparisons to baseline* and 3-month values# and to changes observed in upper body training group@.

men in the same 8–13-week recruit training, and the fractures in women tend to be more debilitating. Pelvic and femoral stress fractures accounted for more than half of the stress fractures in women, whereas for men, femoral fractures were uncommon, and pelvic fractures were not observed.[19,23–25] Stress fracture has not been well studied outside of the military because it is somewhat unique to the concerted ramp-up in physical activity of recruits, which triggers changes in bone metabolism and fracture vulnerability. The special military prevalence of this debilitating injury made stress fracture prevention a key target of the DWHRP, with an opportunity to benefit all active women.

Thousands of female Army, Navy, and Marine

Corps recruits were studied prospectively for stress fracture in DWHRP studies, most consistently revealing low aerobic fitness and injury history as risk factors.[19,23,26] Bone responses during basic training indicated that young women build bone differently from young men in response to the forces acting on their bodies, with women building bone on the endocortical surface and men responding on the subperiosteal surface. Female trainees who fractured tended to have lower bone mineral density (BMD) compared with female controls,[23,26] and also smaller diameter bones with thinner cross-cortices, explaining some of the increased risk in terms of bone geometry[26] (Fig. 3). Resistance training produced significantly greater increases in spine and femoral bone density compared with the improvements produced by an aerobic exercise program.[27]

These observations are central to new studies on biomechanical effects on normal bone in the DoD Bone Health and Military Medical Readiness (BHMMR) research program that targets effective strategies to strengthen bone and eliminate the risk of stress fracture during basic training while also reducing risk of osteoporosis later in life. Since 1997, this program has expanded on the initial investment in DWHRP stress fracture studies to include $35M in special congressional appropriations funding 40 major projects on bone physiology and stress fracture. The DoD also joined with other federal agencies to update dietary reference intake values, leading to a significant revision of calcium requirements for young women, based primarily on bone health outcomes and considering upper limits of safety. Several identified research gaps are being addressed in the BHMMR program, and the results will translate into practical calcium and vitamin D supplementation guidance for military women (e.g., policy recommendations from the DoD Nutrition Committee; update of Military Dietary Reference Intakes in the joint service regulation on nutritional requirements; and/or inclusion of operational ration supplement packets).

MEDICAL SURVEILLANCE DATABASES

One of the greatest accomplishments of the DWHRP was the development of better injury and illness epidemiological tools. This effort recognized the critical importance of a medical surveillance database system to identify problems and explore their causes.[28] For the first time ever, researchers were able to measure hospitalization rates for men and women by diagnostic codes across services and job classifications.[28,29] This was accomplished through Navy medical leadership that made epidemiological research the single most important priority for Navy intramural

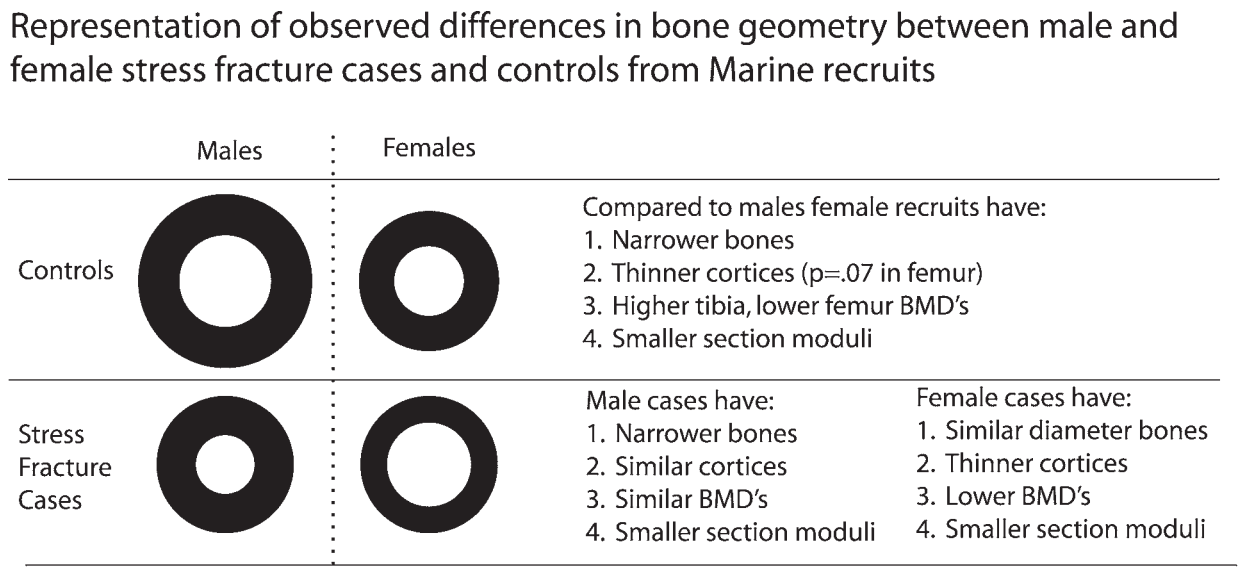

FIG. 3. Schematic of observed differences in bone geometry between male and female stress fracture cases and controls from a large sample of Marine recruits (reproduced with permission from the ref. 26). Differences are exaggerated in this illustration for clarity. These data indicate the importance of bone geometry, separate from BMD, in fracture susceptibility.

DWHRP projects. Navy researchers designed a prototype epidemiological database architecture that attempted to standardize coding of hospitalizations, linked individual career and medical histories and other available data, and cross-mapped data elements with equivalent data in other services. Research access to the Career History Archival Medical and Personnel System (CHAMPS) was enhanced with improvements in the Epidemiological Projection Interactive System (EPISYS) user interface that calculated age-adjusted incidence rates from CHAMPS (Fig. 4). This demonstration project was able to compare hospitalization rates for Air Force, Army, and

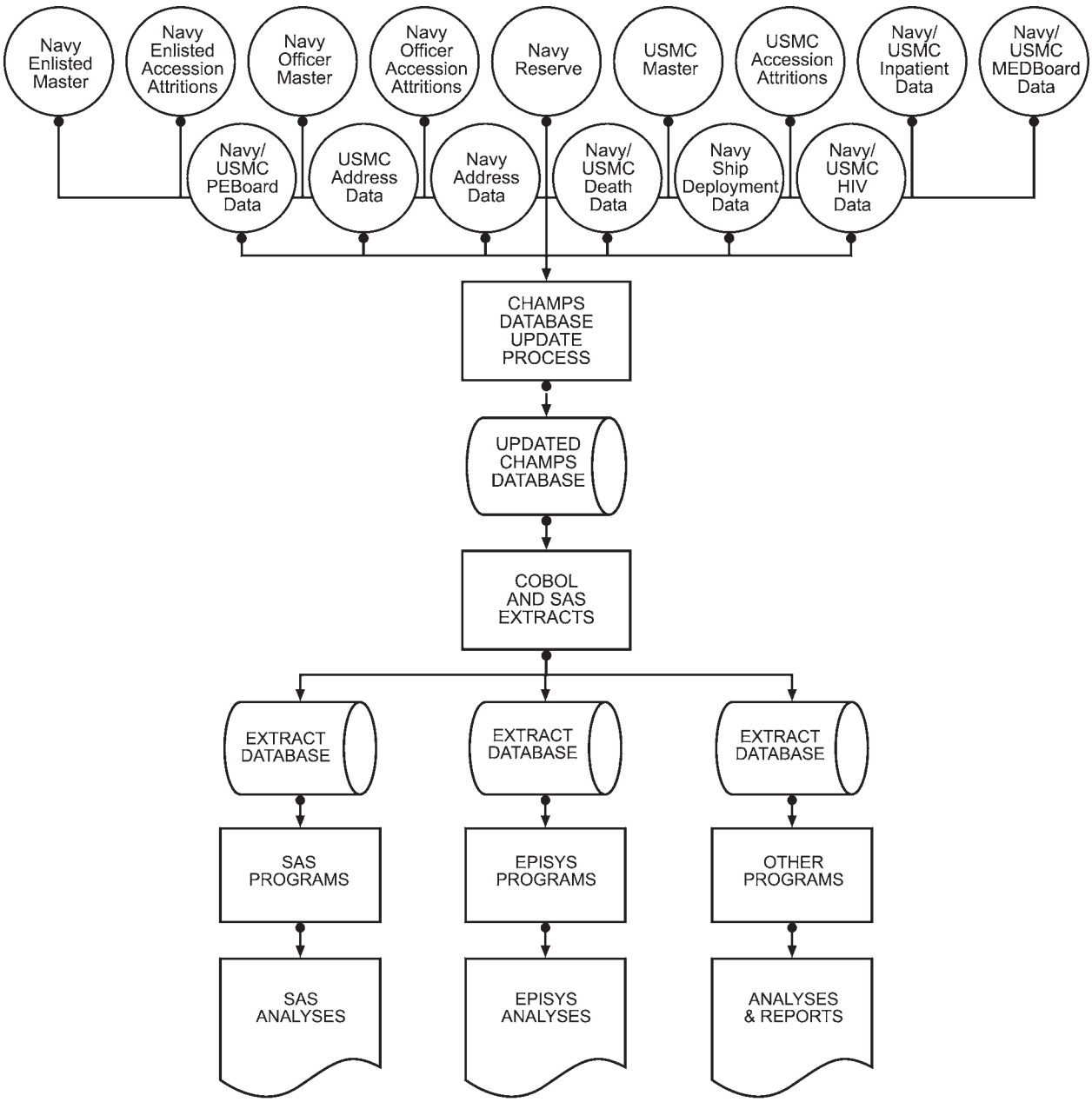

FIG. 4. Example of the data flow in the original conception of medical data capture into a central database based on the Navy-led effort using the Career History Archival Medical and Personnel System (CHAMPS) with improvements in the Epidemiological Projection Interactive System (EPISYS) user interface (reproduced from the technical report, ref. 28). This demonstrated the feasibility and usefulness of such a system and led to establishment of the DoD-wide Defense Medical Epidemiology Database (DMED).

Navy enlisted active duty women.[28] It also provided an epidemiological base for two other interrelated DWHRP efforts that studied medical problems of women aboard ships[29] and examined illness, injury, and attrition in female trainees.[19] These precursor demonstrations contributed to the creation of the Defense Medical Epidemiology Database (DMED) in 1996. The DMED standardized epidemiological reporting across services and provides an Internet-based interface for researchers to access key data (e.g., demographics, assignments and deployments, hospitalizations, outpatient visits, immunizations, deaths) in the Defense Medical Surveillance System (DMSS). These DWHRP efforts also helped to develop the infrastructure that led to the establishment of the DoD Center for Deployment Health Research (at the Naval Health Research Center) by the assistant secretary of Defense for Health Affairs in 1997. The DoD Medical Surveillance Center (at the U.S. Army Center for Health Promotion and Preventive Medicine) was established at the same time, with antecedents in the DWHRP exploratory efforts to develop DoD-wide epidemiological tools.

A separate epidemiological effort linked Army databases, including such service-unique data as the Health Risk Appraisal, to provide an experimental tool to further improve medical surveillance approaches. The Total Army Injury and Health Outcomes Database (TAIHOD) has been used to explore longitudinal associations between personal characteristics and demographics, and longer-term outcomes, such as disability discharges,[8,30] and risk-taking behaviors and motor vehicle accidents.[31] Some of the studies further refined the methodology to improve the quality of data in the surveillance databases for future efforts, including NATO standardization of injury coding.[32,33] Other collaborative efforts using the TAIHOD have examined gender differentials for a wide variety of occupational injury rates, such as parachute injuries,[34] sports and physical training injuries,[35–37] carpal tunnel syndrome,[38] and ocular trauma.[39]

DWHRP-sponsored databases revealed similar injuries and illnesses for men and women across military services after obstetric and gynecological conditions were excluded.[7,20,29] This is illustrated in Table 4 in a list of top diagnoses for hospitalized enlisted female soldiers. These reflect medical conditions associated with a healthy, young, active population. Pregnancy and associated factors contributed to nearly half of female hospitalizations in the Army,[7] Navy,[29] and Air Force.[20] These factors also explained more frequent grounding (>30 days) of female Air Force pilots.[40] The highest incidences of hospitalized injuries were related to sports and physical training activities, with knee and other joint problems at the top of the list.[36]

GENDER-APPROPRIATE PERSONAL READINESS STANDARDS

Resolving inconsistent body composition, fitness, and nutrition standards

In 1994, policies and standards for servicewomen were extensions and piecemeal amendments of the rules and data established for men. This produced some strange inconsistencies that could be expected to compromise rather than enhance readiness. For example, all servicewomen were encouraged to strive for inappropriately low body fat (26%), apparently based on a perception that physical performance might be closer to that of males if body fat were closer to that of male-appropriate levels.[41] At the same time that women were prompted to restrict dietary intakes to meet unrealistic body fat standards, they were issued field rations that provided nearly 4000 kcal/day while their actual requirements were probably about 2800 kcal/day. The packaging lacked nutrition information, so service members, including the 10%–20% of marginally iron-deficient women and perhaps a greater proportion of women with deficient calcium intakes, had no easy way to determine which components of the ration were important to consume.[42,43] Even the measurement of body fat was problematic. Whereas total body fat in males is readily approximated by an abdominal measurement, there is no single site of female fat deposition, as evidenced by the independent development of four very different female body fat equations by the services. Low body weight, as well as dietary restriction attempts to achieve excessively low body weight, reduce strength capacity. This may also reduce BMD,[44] placing servicewomen at greater risk for stress fracture and, later in life, for osteoporosis. At any given time, 10% of servicewomen are pregnant, and some may be overly restricting weight gain, compromising their own

TABLE 4. TOP 40 CAUSES OF HOSPITALIZATIONS FOR FEMALE ENLISTED SOLDIERS, 1990–1994, IN ORDER OF RATES (PER 10,000 PERSON-YEARS)

Diagnosis	*Rate: women*	*Rate: men*[a,b]
1. Early or threatened labor	163	—
2. Normal delivery	129	—
3. Delivery trauma (perineum, vulva)	125	—
4. Fetal and placental problems	110	—
5. Contraceptive management	92	24 (#7)
6. Adjustment reaction	83	40 (#2)
7. Labor problems	82	—
8. Spontaneous abortion	79	—
9. Other mother conditions	75	—
10. Umbilical cord complications	74	—
11. Pelvic inflammatory disease	69	—
12. Pain, female genital organs	67	—
13. Viral and chlamydial infection	67	21 (#8)
14. Disorders of tooth eruption	59	33 (#5)
15. Noninfectious gastroenteritis	51	19 (#9)
16. Eclampsia, preeclampsia	50	—
17. Excessive vomiting in pregnancy	49	—
18. Pelvic soft tissue abnormalities	45	—
19. Other pregnancy complications	45	—
20. Other problems, amniotic	44	—
21. Other, abdominal/pelvic symptoms	44	10 (#34)
22. Other, synovium, tendon, bursa	37	18 (#10)
23. Acquired deformities of the toe	33	10 (#31)
24. Fetal malposition and malrepresentation	33	—
25. Antenatal screening	32	—
26. Ectopic pregnancy	32	—
27. Infections of the kidney	31	(not in top 40)
28. Internal derangement of the knee	31	50 (#1)
29. Other obstetric trauma	30	—
30. Noninflammatory, ovary, fallopian tube	29	—
31. Missed abortion	28	—
32. Dentofacial anomalies, malocclusion	27	11 (#29)
33. Acute upper respiratory infections	25	13 (#22)
34. Evaluation of suspected conditions	25	9 (#38)
35. Alcohol dependence syndrome	24	40 (#3)
36. Intestinal infections, other organisms	24	9 (#36)
37. Other, labor/delivery complications	24	—
38. Acute pharyngitis	23	15 (#16)
39. Infectious/parasitic conditions, mother	23	—
40. Prolonged pregnancy	22	—

From reference 7.

[a]Rates and relative occurrence of diagnosis in a comparable list for male enlisted soldiers are shown for comparison.

[b]Not in the top 40 for women are #4, inguinal hernia (34 hospitalizations/10,000 person-years for men) and #6, other—derangement of joint (25 hospitalizations/10,000 person-years for men).

health, lowering birth weights of their infants, and actually increasing risks for obesity in their children later in life.[41]

To address these issues, the Institute of Medicine (IOM) was commissioned to assess the impact of current regulations, standards, and policies on military readiness of servicewomen.[41] This Body Composition, Nutrition, and Health (BCNH) of military women committee was also asked to provide recommendations to fix inconsistent or conflicting standards. As one example of their recommendations, the committee proposed an approach to a single DoD standard for female body fat and a novel solution to mismatches between body fat standards and fitness test performance[41] (Fig. 5). This has been considered by each of the services, and elements of the recommendation, such as a single method of body fat measurement and a universal lower boundary of screening weights (i.e., no service

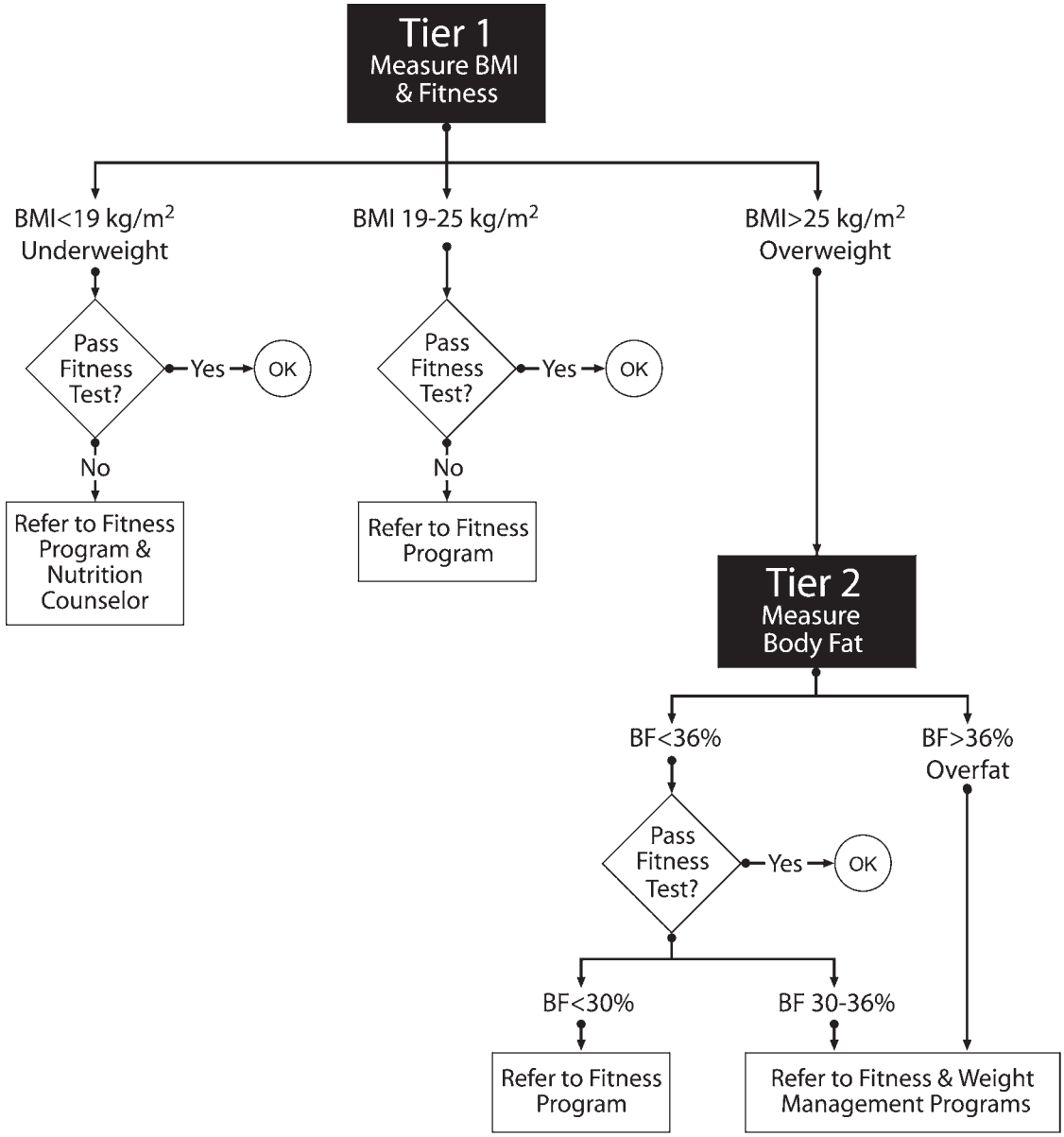

FIG. 5. Fitness and body composition evaluation scheme proposed by the BCNH of the Institute of Medicine.[41] The committee recommended age-independent limits of BMI of 25 kg/m^2 and 36% body fat for all servicewomen. A particularly novel recommendation was the linkage between fitness test performance and body fat standards, permitting a fit fat gray zone between 30% and 36% body fat; women below 30% body fat were not candidates for weight management. Various elements of these recommendations were incorporated into the Defense-wide Instruction (DODI 1308.3) and regulations of each of the services.

should make screening table weights for either gender more stringent than the currently regarded healthy weight, a body mass index [BMI] of 25 kg/m^2), have been incorporated into a revised DoD Instruction. Other recommendations have been implemented, such as nutrition labeling of operational rations to indicate which components of the meal contain key nutrients and minerals; this is helpful to individuals interested in making an informed choice about their nutrient intakes.

Exercise intensity and energy balance

In the last century, it was often said that it might be harmful to a woman's health to exercise too hard, and at the start of the DWHRP, it was still generally accepted that intensive exercise

could cause menstrual abnormalities in healthy young women. The female athletic triad was a concept that excessive exercise could induce amenorrhea, with a resulting decline in estrogen exposure that would lead to bone loss and increased risk of osteoporosis. This theory was influenced by studies of anorexic women using both exercise and dietary restriction to achieve abnormal thinness. In a series of very precisely controlled studies, moderate levels of exercise by young women did not, in fact, produce the changes that would lead to reproductive dysfunction, as long as energy requirements were met[45] (Fig. 6). This very important project demolished an incorrect assumption that female soldiers should be excluded from high-intensity training for reproductive health reasons. Subsequent to the finding that increasing levels of energy deficit disrupt menstrual regulation, this study also demonstrated that markers of bone formation were suppressed within 5 days in the follicular phase of the menstrual cycle when energy deficits became large enough to suppress estrogen production. Bone formation appeared to be more sensitive to energy deficit than markers of bone resorption, indicating the potential for near term loss of bone with severe dieting.[44] This study suggested reasonable limits for sensible weight loss programs, within which adverse consequences, such as bone mineral loss, might be avoided.

Another carefully controlled laboratory project investigated gender-related aspects of substrate utilization and energy metabolism with exercise and dietary restriction relevant to high-intensity military training. Women can better survive extended periods of energy deprivation in part because of larger fat stores, but differences in substrate utilization during energy expenditure have not been well defined and might be important to the design of weight loss programs or the composition of survival rations. This study included

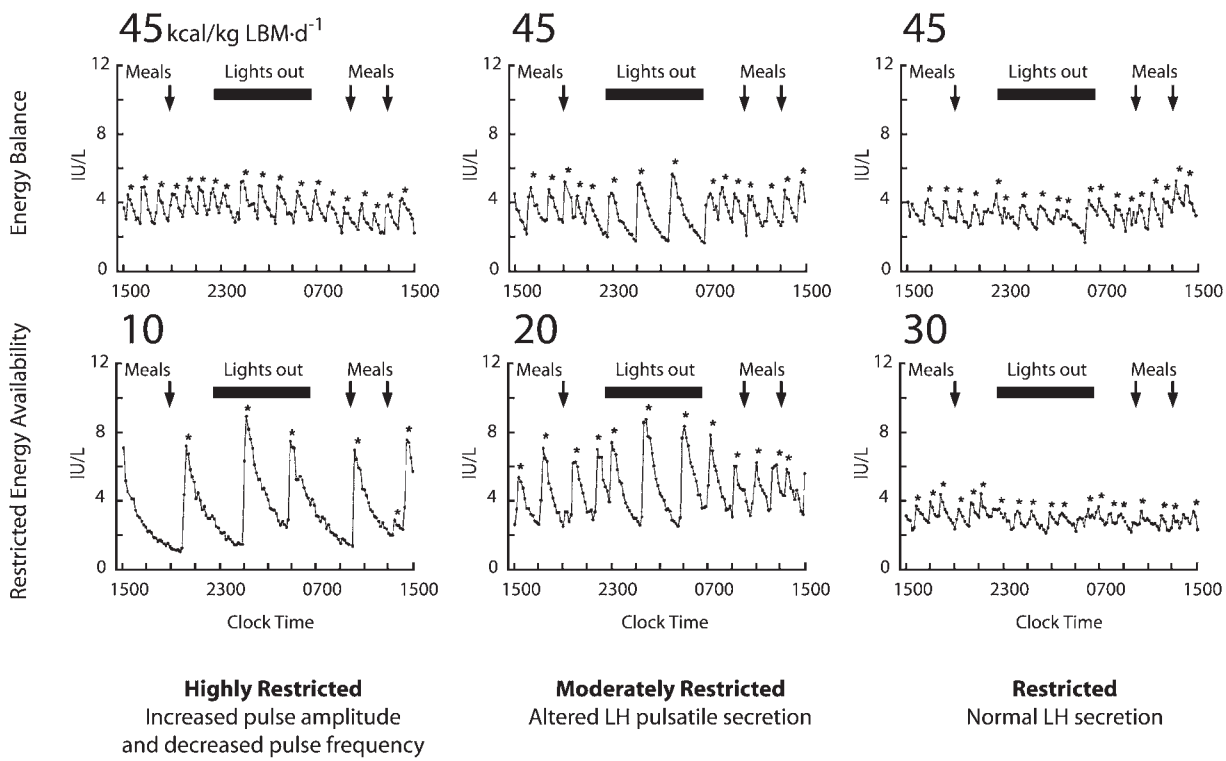

FIG. 6. Patterns of pulsatile luteinizing hormone (LH) release in response to different levels of energy balance, comparing adequate intakes (+45 kcal/kg lean body mass [LBM]/day, or approximately 2000 kcal/day) to deficient balances for the same individual (+10, +20, and +30 kcal/kg LBM/day) (reproduced with permission from the ref. 45). The pattern of decreased pulse frequency and increased amplitude at 10 kcal/kg LBM/day indicate disruption of reproductive cycles at specific thresholds of energy deficit. These elegant studies demonstrated that energy deficit, not intensity of exercise, is the important determinant of menstrual disturbances and that there are reasonable limits of energy deficit that should not be exceeded in weight loss programs.

detailed tracer studies to assess amino acid, lipid, and glucose metabolism, measurements of total energy expenditure, and physical and neuropsychological testing during 3 days of starvation and 3 weeks of semistarvation (at 70% of requirements). Preliminary analyses suggest no major differences in metabolic responses between males and females.[46]

Postpartum return-to-duty standards

Surprisingly little information is available on the nature of body composition changes and energy requirements through pregnancy and in the postpartum period. There was so little information on occupational standards for postpregnancy management that at one point, one service established a postpartum return-to-duty policy by arbitrarily splitting the difference between two existing policies that allowed 3 and 6 months to meet standards. This gap was addressed by a DWHRP project that produced important information that will influence national and international guidelines for energy requirements of women through the pregnancy-lactation cycle.[47,48] These comprehensive studies were based on women recruited from the National Guard who intended to become pregnant and included detailed examination of the body composition of their newborns. Among other findings, the studies support a postpartum return-to-duty body composition standard of at least 6 months. In one group of normal-weight women (defined in this study by a BMI of 20–26 kg/m^2) starting with an average 28% body fat, percent body fat increased early in the postpartum period, followed by a high rate of fat loss between 3 and 6 months in the postpartum period (Fig. 7). During pregnancy, these women gained an average of 30 pounds, including 10 pounds of fat weight. Women exceeding current gestational weight gain guidelines had the greatest 6-month postpartum fat retention.[47,48] Underweight women (BMI<20 kg/m^2) tended to retain more of their pregnancy fat gain at 6 months postpartum, suggesting achievement of more appropriate body composition following pregnancy, and a third group of overweight women (BMI>26 kg/m^2) tended to return to their prepregnancy body composition. No major differences were noted in postpartum body composition changes in breastfeeders compared with those who discontinued or never breastfed their babies.[47] This study also produced important new data on actual energy requirements of active women.[49]

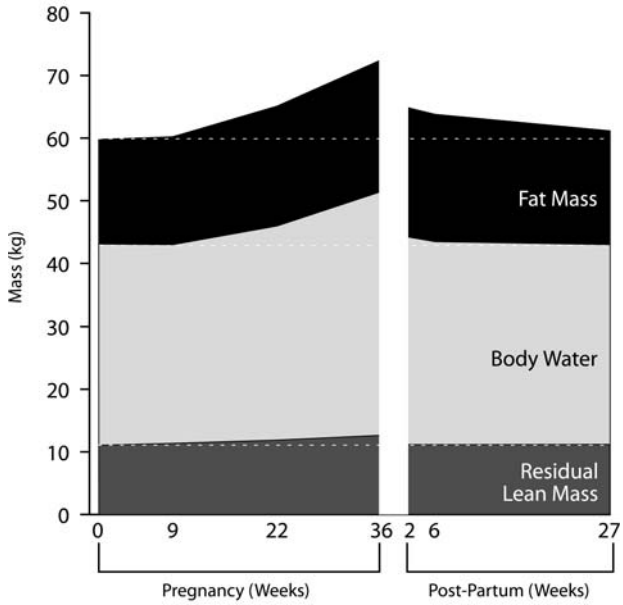

FIG. 7. Changes in body composition in normal-weight (BMI 21–26 kg/m^2) health women through pregnancy and the postpartum period.[47] Residual lean mass includes bone mineral and chemical components other than body water. Total body potassium, nitrogen, body water, and bone mineral were all measured in this study, but because of the potential risks to a fetus, some of these measures were only made before and after pregnancy. Two other groups were studied (data not shown), including underweight women who retained more of their fat gain at 6 months postpartum, and overweight women who, like the normal-weight women shown here, had nearly returned to prepregnancy fat levels by 6 months postpartum. Overall, women remaining within gestational weight gain guidelines produced normal-weight newborns and were most likely to return to prepregnancy weights by 6 months postpartum.[47]

The same study considered strength and maximal aerobic capacity changes in the postpartum period, finding significant declines 6 weeks postpartum, with only some recovery by 27 weeks, compared with prepregnancy strength and aerobic capacity measures. Some of this was attributed to changes in types of physical activity, which shifted from conditioning and occupational activities prepregnancy to walking and home activities postpartum.[50] A separate major study on postpartum return-to-duty fitness discovered that half of pregnant soldiers failed to return to their prepregnancy fitness levels 6 or 9 months postpartum, and postpartum soldiers were four times more likely to fail the first postpartum fitness test than nonpregnant soldiers,

supporting the need for graded postpartum fitness programs specifically targeting this population.[51]

Breastfeeding in the postpartum period has been widely recommended for the health of the infant[41] but may also have important effects on emotional status and stress responses for the mother affecting the return-to-full-duty status. The reduced estrogen levels in postpartum lactating women may lower stress reactivity, comparable to the effects that have been reported elsewhere for women in the early follicular phase of the menstrual cycle. In a series of exercise stress challenges in postpartum women, nonlactating (bottle-feeding) postpartum mothers had higher blood pressure, decreased vagal tone, and larger stress hormone responses.[52] Lactation decreased physiological indicators of stress reactivity and increased the maternal bond with the infant.[53,54] This information provides one more reason to facilitate servicewomen breastfeeding during their initial return to duty, 3–6 months postpartum, as recommended by the IOM.[41] The committee did note that no statistics are available on breastfeeding by active duty mothers, and this was not resolved by any DWHRP studies.

PROTECTION AGAINST HAZARDS TO REPRODUCTIVE HEALTH

Pregnancy rates and complications

Pregnancy rates (point prevalence) in military women have been generally reported to be around 10%; at least half of these pregnancies are unplanned. The potential for pregnancy complications that may be difficult to diagnose and manage in assignments remote from medical care, such as ectopic pregnancy, had been suggested to present a risk that was too high to place women in certain assignments, such as aboard strategic submarines. However, the rates of risk were unknown. A large sampling in the Navy's Hospitalized Pregnancy and Women Aboard Ship studies provided estimates that if pregnant women remained aboard ships for their first 20 weeks of pregnancy, approximately 9 ectopic pregnancies (~2.5% of pregnancies) and 40 spontaneous abortions (~12.5% of shipboard conceptions) would occur at sea each year.[55] Pregnancy and pregnancy complication rates vary in other circumstances; for example, pregnancy rates declined in a previous study with longer at-sea deployments during higher combatant operational tempo.

Several previous studies have reported higher risks of preterm delivery and lower birth weights in active duty women, even when compared with other women treated within the same medical facilities, and these findings have never been adequately explained. A prospective sampling of birth outcomes at five Army posts compared active duty soldiers with family members and compared outcomes by military occupational specialties.[56] There were no differences between jobs in preterm births or underweight newborns after adjustment for key covariates, such as mother's age, race, and smoking history. The incidence of spontaneous abortion was also similar between nonsoldiers and soldiers (~8%–9%) in most job categories, with the exception of a significantly elevated incidence associated with logistics jobs (which encompass a broad variety of specialities, ranging from fuel handlers to medical supply specialists).[56] This latter finding has yet to be confirmed in a study focused on this question and carefully controlled for demographic differences. A detailed assessment of the work and emotional environment of 350 active duty pregnant women from all four services demonstrated that preterm deliveries were most closely associated with marital status, with single military women at greater risk than married women.[57] Bacterial infections and intraamniotic infection were investigated as another explanation for preterm labor. Although the prevalence of bacterial vaginosis was relatively high (27%) in a large sample of military women,[58] infection rates were low in a group of women with subsequent preterm births.[59]

Sexually transmitted disease and unintended pregnancy evaluations and interventions

More than one third of Navy women expressed their intent to become pregnant within a year; however, half of the sexually active women who were not using contraception also did not hope to become pregnant.[60] Unintended pregnancy and sexually transmitted diseases (STDs) can have major effects on unit readiness. Stealth STDs, such as asymptomatic *Chlamydia trachomatis* infections in young women, can produce pelvic inflammatory disease (PID), infertility, and ectopic pregnancy, reiterating the importance of STD and unintended pregnancy prevention. Although most ships were found to have training

programs for birth control (90%), STD prevention (97%), and Navy pregnancy policy (84%), the availability of contraceptives, pregnancy tests, and STD tests was limited.[61] Similar issues were highlighted for the other services in similar studies,[56] suggesting a need for more effective healthcare delivery to women, especially single women living in the barracks or onboard ship, where there are numerous barriers to access to reproductive services. The Navy studies produced specific and substantive recommendations to enhance healthcare for women aboard ship based on surveys of women as well as healthcare provider experience and expert opinion.[60–62]

A sample of 13,204 female Army recruits not seeking medical treatment was screened for *Chlamydia* infection and found to have a 9.2% infection rate, with 12.2% in 17 year olds and 15% or more in recruits from five southern states.[63] This was at least twice the rate reported in national surveys. Significant risk factors for infection included frequent sex, multiple partners, absence of condom use, ethnicity, and young age[63] (Fig. 8). The testing method (urine-based ligase chain reaction) was developed as a cost-effective method to screen for *Chlamydia* in asymptomatic women from simple urine specimens.[64,65] Detailed economic analyses of three different options, targeted screening, universal screening, and universal antibiotic treatment of recruits with azithromycin, led to a suggestion that mass therapy of a well-defined cohort at high risk for *Chlamydia* infection might be considered as a cost-effective measure, with estimated public health savings of greater than half a million dollars per 100,000 female Army recruits.[66,67] Other studies of active duty Navy females and Marine Corps males revealed rates as high as 7% and further demonstrated the practical use of the new testing methods.[62,68,69] *Chlamydia* infection has specific health risks to servicewomen, but as an indicator of risky sexual behavior, it raises concerns about rates of a wider range of STDs.

Within the first year of service, Marine Corps women had a pregnancy rate of 18%, of which two thirds were unintended; 57% of women who engaged in sexual intercourse in the month prior to enlistment reported that they did so under the influence of alcohol or drugs; 14% of the women had sexually transmitted infections, and 27% had

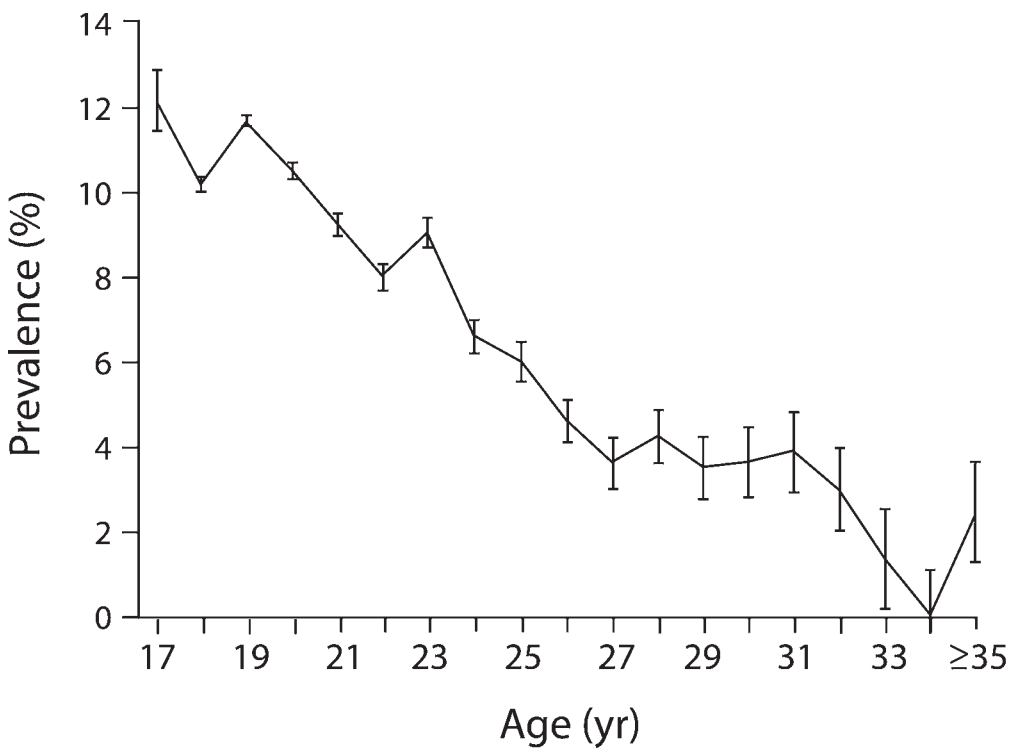

FIG. 8. Age-specific prevalence of *Chlamydial* infection among 13,204 female Army recruits, based on a urine ligase chain reaction assay (reproduced with permission from the ref. 63). Young age was one of the most important risk factors for *Chlamydia* infection in female recruits.

bacterial vaginosis.[58,69] Helping young service members make informed decisions about their health and fitness was the subject of a difficult but important DWHRP study. This was the first randomized, controlled trial to demonstrate that a health education program for military recruits could have long-lasting benefits, carrying out more than a year after the training[70] (Fig. 9). A

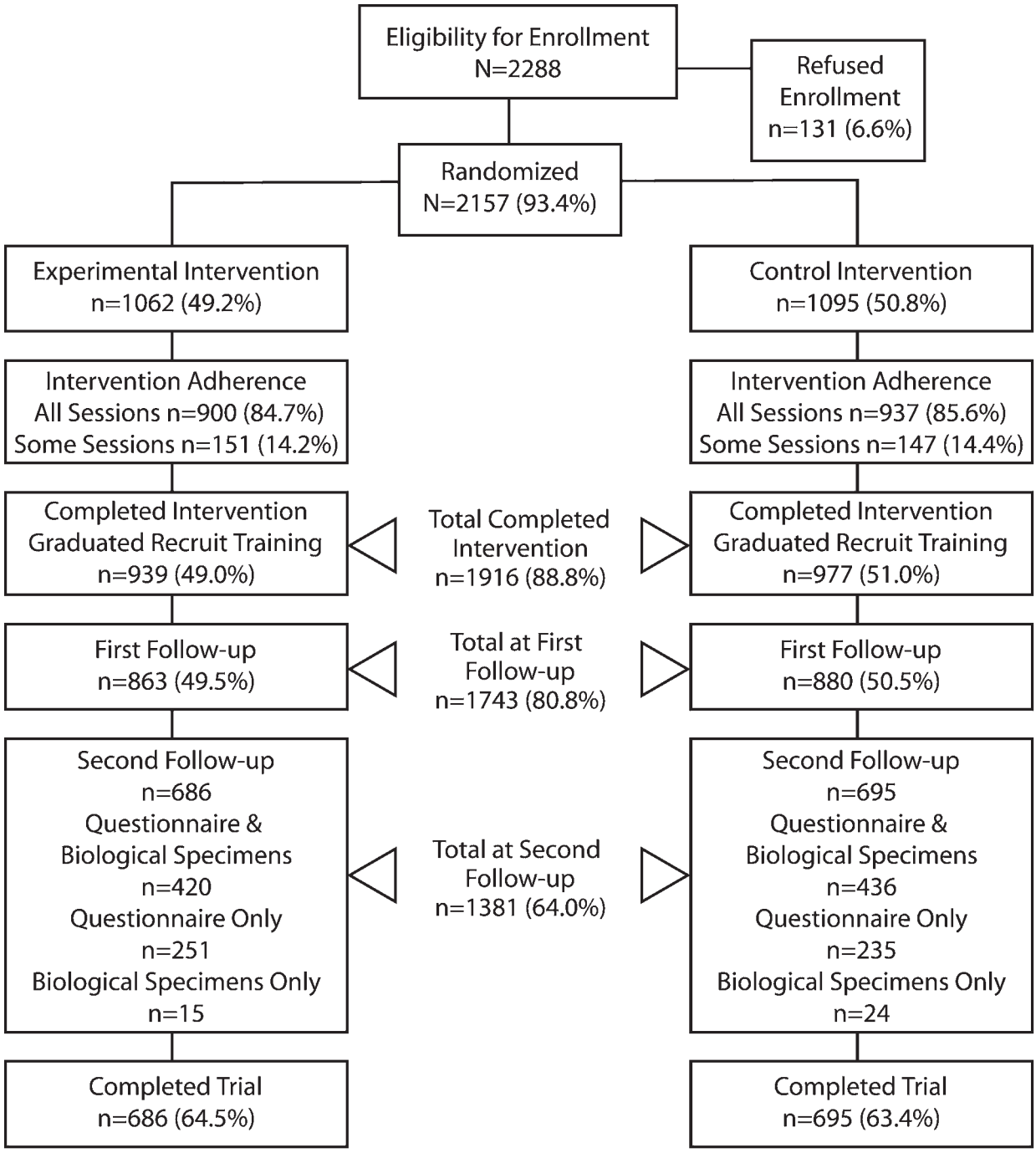

FIG. 9. Testing scheme in the randomized controlled trial of a health risk education program developed for STD/UIP prevention in female Marine recruits (modified from the original; used with permission from ref 70). This flowchart illustrates the challenges in retaining test participants in any rigorous evaluation in a military setting. This study with Marine recruits probably reflects optimal success rates for such a study; 73% of recruits completing the experimental intervention completed the trial despite the presence of reservists and other uncontrollable study losses. The study results demonstrated long-term reduction in STD reinfection rates with a specially developed intervention.

training program was developed based on the information, motivation, and behavioral skills model that has been effectively used in AIDS-preventive behavior. This included training on responsible sexual behaviors, prevention of STDs and unintended pregnancy (UIP), and associated risks of alcohol abuse conveyed through such techniques as role playing and custom-developed videotape dramatizations. In this carefully designed study, testing conducted more than a year after the training revealed an effective reduction in STD rates in the group of women at risk.[66] Overall, 14.5% of women tested postintervention had STDs, and 7% had positive pregnancy tests and stated that the pregnancy was unplanned. Combined rates of these adverse reproductive outcomes were significantly lower in the experimental intervention groups (17.9%) compared with the control (nutrition and injury reduction training) group (23.9%). The impact of the training was particularly noticeable in the one third (35%) of recruits who reported unsafe sexual behaviors but had no history of pregnancy or STD; by 1 year postintervention, 8% of this subset of studied recruits had been infected with an STD compared with 22% of this subset of the control group.[66] The training program was implemented for female recruits at Parris Island. A new study is planned to examine the effect of coed training (comparing gender-segregated training in the Marines to integrated training in the Army) and generalizability to an Army training setting and will include sexual violence prevention as part of the instruction. This represents a DoD breakthrough in the commitment to properly conducted health risk communication science.

Non-STD infectious disease threats to reproductive health

Some infectious diseases of military importance (e.g., acutely incapacitating endemic diseases, such as malaria) are a special threat to pregnant women, as are some of the preventive measures and treatments. Mefloquine is used because of its effectiveness against chloroquine-resistant *Plasmodium falciparum*. However, it is not known to be safe for use in pregnant women, and there was no health risk communication plan for female users when it was administered during the 1992–1994 deployment to Somalia. Seventy-two female Soldiers who may have inadvertently exposed their fetuses by becoming pregnant either during or shortly after mefloquine use were enrolled in a special Army registry.[71] Although no congenital malformations or abnormal rates of preterm deliveries were identified, this highlighted the need for greater care in the area of health risk communication that would ensure that servicewomen understood the potential risks and would allow them to make informed pregnancy decisions.

Azithromycin is considered safe for use during pregnancy (pregnancy category A drug) and was shown to be at least as effective as doxycycline in DWHRP effectiveness against mefloquine-resistant malaria in an area of intense malaria transmission in Kenya[72] and against two strains of scrub typhus in northern Thailand.[73] This demonstrated the availability of alternate pregnancy-safe preventive measures for women.

Insect repellents, primarily formulations with DEET, have been shown to be effective first lines of defense against the vectors (mosquitoes, ticks, and sandflies) of some of these endemic diseases. However, the efficacy and metabolism of DEET in females is relatively unstudied. In a comparison study, a DEET-containing topical repellent (extended duration tropical insect/arthropod repellent) was shown to provide significantly less protection over time for women compared with men, with less than the advertised 95% protective efficacy after 6 hours for women.[74] Other studies suggest changes in attractiveness to mosquitoes as a result of estrogen fluctuations and amino acid secretions, although, estrogen levels of the women did not correlate with an increased number of mosquitoes feeding in this study. DEET formulations appear to be metabolized and released at a higher rate in women for reasons that still remain unknown. Higher sweat rates in men would lead to a prediction that men would be more likely to lose protection from a given dose of DEET before women.

Malaria is itself a specific risk to women during pregnancy because of sequestration of the infected red cells in deep vascular beds of the placenta and is a major cause of pregnancy-related complications in endemic areas. A DWHRP study established that this special malaria susceptibility was associated with adherence of *Plasmodium falciparum* parasites to a molecule in the human placenta.[75] Protective antibodies are present in women in endemic areas who have had previous pregnancies, but

new mothers appear to lack antibodies to the specialized subset of parasites that attack pregnant hosts[76,77] (Fig. 10). These discoveries pave the way for development of a vaccine for maternal malaria. The researchers went on to propose an explanation for the poor fetal outcomes from infected primigravidas, where the fetus is usually not malarial but is adversely affected by the maternal biochemical response that is conflicted between appropriate pregnancy and infectious agent responses.[78]

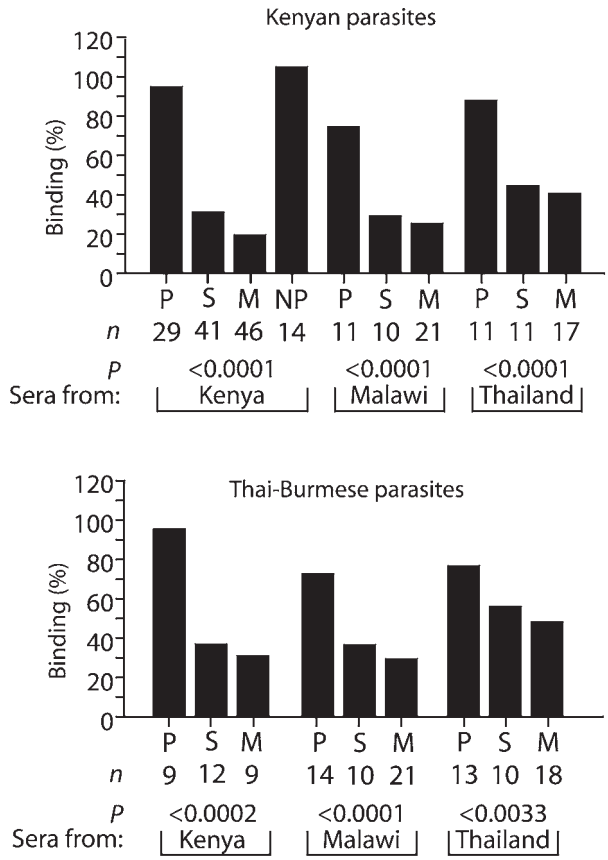

FIG. 10. Serum inhibition of malarial parasite binding to chondroitin sulfate A, expressed as a percentage of binding in control serum for primigravidas (P), secundigravidas (S), multigravidas (M), and males (NP)(reproduced with permission from ref. 77). These data demonstrate that maternal antiadhesion antibodies that develop in women after a first pregnancy in endemic areas are effective against a wide range of malaria parasite strains, making possible the development of a generic antiadhesion vaccine. Other data from this project demonstrated significant consequences of maternal malaria to maternal and infant health.[78]

Fertility biomonitoring study designs and methods development

Of the important concerns in military women's health, reproductive fertility is one of the most difficult to assess because of the number of factors involved in successful conception and implantation. Disruption of normal menstrual cycles provides one type of indicator of a reproductive hazard. Hormone pulsatility studies are a sensitive measure of menstrual disruption but are not practical in a field environment. A DWHRP-sponsored SBIR project attempted to develop a semiquantitative test strip for a pregnanediol-3-glucuronide, a principal urinary indicator of progesterone metabolism. This could be a useful adjunct to current measures for detection of effects on menstrual cycles because various stressors may cause a shorter (and deficient) or longer luteal phase without completely abolishing cyclicity. Unfortunately, performance of the final product fell short of expectations. A separate study using laboratory-based measures of daily urinary excretion rates of estrogen and progesterone metabolites found no notable effects on the menstrual cycles of Air Force women with demonstrated occupational fuel and solvent exposures[79,80] (Fig. 11).

Another ambitious study attempted to assess the effects of ionizing radiation exposure in flight attendants as an indicator group for women in aviation. Flight crew members studied in one group incurred an estimated average dose of 1.5–1.7 mSv, with some individuals reaching 3.5 mSv (pregnancy limits are 1 mSv to the conceptus).[81] Design challenges in matching factors related to activity and diurnal rhythms disruption proved to be very difficult in comparison to lower exposure nonmobile groups. Reproductive biology parameters measured in daily urine and saliva samples through one menstrual cycle in flight attendants were compared to those of schoolteachers from the same home regions.[82–84] No specific conclusions could be reached about radiation risks to fertility even though flight attendants had a very high perceived risk.[84] Additional laboratory studies of environmental hazards to ovarian function and early embryo survival are needed to identify potential reproductive risks or allay fears about occupationally unique exposures, such as toxicological (e.g., fuels and solvents), biodynamic (e.g., impulse

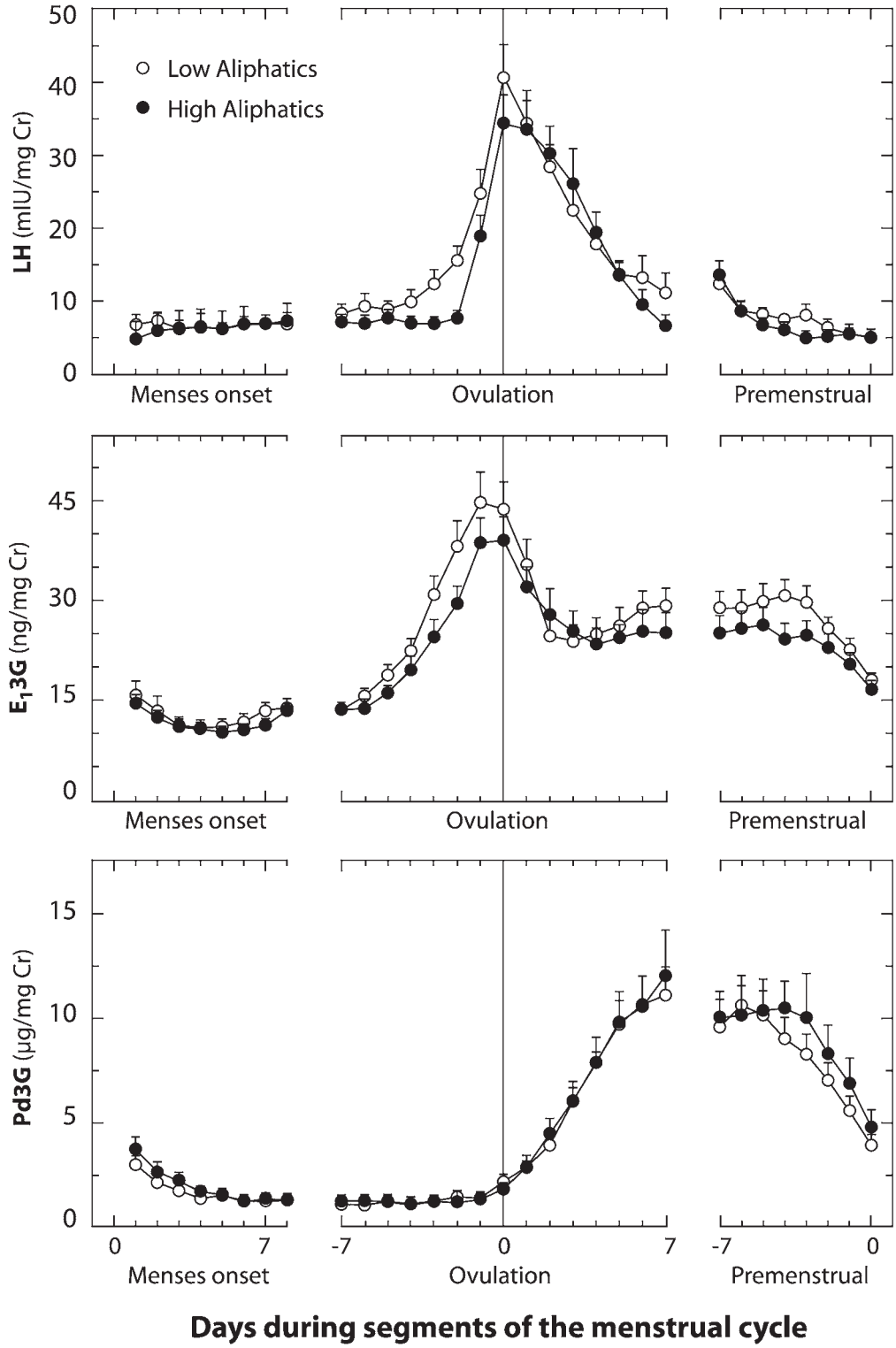

FIG. 11. Comparison of urinary indicators of menstrual status through menstrual cycles in Air Force women with low (n = 31) and high (n = 32) total aliphatic hydrocarbon breath analyses (reproduced with permission from ref. 79). The graphs show creatinine-adjusted urinary concentrations of luteinizing hormone (LH), estrone-3-glucuronide (E_1 3G) (a principal urinary metabolite of estradiol), and pregnanediol-3-glucuronide (Pd3G) (a principal urinary metabolite of progesterone) in the two groups. Apparent fuel and solvent exposures did not have any marked effects on one measure of fertility (i.e., menstrual cyclicity).

noise, vibration, and jolt), and radiation (e.g., radiofrequency and ionizing radiation sources) hazards.

SIGNIFICANT CLINICAL ISSUES

Some of the clinical issues that are either unique to women or more prevalent for women have special importance to the military. This includes problems that may not be perceived as priorities in national healthcare but present significant impediments to optimal performance for some military women, ranging from migraine headaches, which are far more prevalent in women than men, to effective management of bacterial vaginosis in unsanitary field environments. Although these issues are also important to women outside of the military, the DoD may have to provide a research leadership role to solve these problems. This was done through creative leveraging of larger medical research funding organizations and industry partners, especially with DoD support, to the generation of preliminary data that would allow investigators to obtain funding for follow-on research. Some examples of these DWHRP projects are summarized here, including management of premenstrual syndrome symptoms, preventing smoking relapse, and concerns about marginal iron and zinc deficiency.

Gynecological and endocrine issues

Menstrual symptoms are debilitating for some military women. One fourth of women in the Women Aboard Navy Ships study reported heavy periods and cramps or pain requiring medication or time off from work. Cigarette smoking was the single strongest factor associated with increased risk of all menstrual symptoms in this study.[85] A large survey of young women in Virginia revealed that 8.3% of women experienced premenstrual syndrome (PMS), with significantly higher rates of alcohol intake in those reporting high stress. The results also suggested the possibility that women reporting PMS exercise more regularly in an attempt to reduce symptoms.[86] A small cross-over study with military women concluded with an important and novel finding that sertraline, a serotonin selective reuptake inhibitor (SSRI), was effective in reducing PMS symptoms when administered only in the luteal phase.[87]

Premenstrual breast pain occurred in 22% of the women in the Virginia study, including many women who did not have PMS but in association with smoking and stress.[88] Breast pain (mastodynia) occurs in 30% of women seen in a breast clinic.[89] A large sample of women using a long-acting progesterone for contraception in Army medical treatment facilities had breast pain only half as frequently as a sample of matched controls, and the severity of the pain was less and less likely to require some form of treatment. Breast pain increased linearly with age; thus, the study concluded that only a small proportion of female soldiers suffer from breast pain severe enough to warrant consideration of intervention and could be effectively treated with mechanical support or anti-inflammatory drugs.[89]

Smoking relapse prevention

Tobacco use is higher in the military than in the civilian population, including 26% of women and 33% of men reporting use of cigarettes within the past 30 days.[90] The Perceptions of Wellness and Readiness Assessment (POWR) study demonstrated that nicotine addiction was more prevalent in military women and that it was associated with other negative health habits, such as alcohol abuse.[91] The study further suggested that this hard core nicotine use was interrelated with other aspects of military culture, adding special challenges to tobacco cessation efforts. This is a significant preventive medicine issue for military women, as other studies of military populations report associations between cigarette use and health problems, such as menstrual symptoms and musculoskeletal injuries. Young Navy women are twice as likely as their civilian counterparts to be hardcore smokers (i.e., regular use with no desire to quit),[92] and this is the group that proved to have the highest smoking relapse following 8 weeks of smoke-free recruit training (90% relapse) and would be the most resistant to any intervention program. A large intervention program with frequent mailouts to provide motivational and behavioral cues for the first 4 months, when relapse is most likely to occur, was unsuccessful based on a 6-month postgraduation survey.[93] Of 5503 female Navy recruits, 42% were self-described smokers at the start of training; 3 months later, one third of all smokers had not smoked in the past 30 days, but the majority (89%) of daily (hardcore) smokers were re-

lapsed.[94] The investigators piloted techniques for enhancing health survey response rates in the military[95] and have continued to investigate more effective methods to eliminate smoking.

Iron deficiency anemia

Women are more likely than men to have iron deficiencies, with 17% of female soldiers manifesting iron deficiencies and 8% meeting criteria for iron deficiency anemia.[43] This is important for servicewomen because of known and suspected impairments that range from disease resistance to optimal mental functioning and physical endurance. Blanket supplementation carries health risks and may ignore important underlying problems. Three major studies were conducted on the health and performance consequences of iron deficiency in military women; unfortunately, the data from these studies remain incompletely analyzed and unpublished. One study of female Army officers found no connection between iron intakes and low hemoglobin nor any simple relationship to physical performance or mood states and reaction time.[42] Extreme dieting for weight loss has been suggested to impair an adequate intake of nutrients, including key minerals; however, the same study did show that reasonable attempts in weight management through the frequent use of reduced fat or reduced energy foods were actually associated with an increased nutrient quality and resulted in higher zinc and iron intakes.[96] A more ambitious study sampled 1210 female Army initial entry trainees, advanced individual trainees, noncommissioned officers, and officers at four sites. The data appeared to indicate a worsening iron deficiency anemia with the progression of training, but an expert review of the available data could not determine the significance of this apparent trend and any potential links to training stressors.[43]

Zinc and iron deficiencies tend to occur in parallel, and these deficiencies and the effects of repletion were the subject of a third major micronutrient study. This study advanced the understanding of zinc metabolism and balance[97] and also suggested some important correspondence between zinc and iron deficiency and neurological and neuropsychological tests (e.g., eye-hand coordination, reasoning, and memory) in young women but requires completion of the data analyses.[98] The extent of physical and cognitive impairment of servicewomen by correctable mineral deficiencies remains an important unanswered question. The causes of the deficiencies also remain unclear but cannot be simply explained away as a normal response to stressful training or attributed to heavy menstrual blood loss. A clinical study with 19 female patients at a military treatment facility suggested that iron deficiency anemia in young women is frequently traceable to upper gastrointestinal disease, even in the absence of digestive complaints and after many of these cases were attributed to menstrual blood losses.[99] This indicates the need for further clinical evaluation of women with iron deficiency that remains refractory to iron supplementation. Recommendations from the Committee of Military Nutrition Research (IOM) later this year are expected to provide substantive guidance to a new Army initiative in this area of mineral metabolism research.

Other clinical issues

Many other DWHRP projects addressed orphan clinical issues for military women that were not actively supported in other research programs, including those in the DoD. For example, most of the focus on HIV a decade ago was on male transmission, with relatively little consideration of infected women in the military program. HIV-1 disease progression was followed in an Air Force active duty population, with comparison between women and men to develop new testing methodology.[100,101] DWHRP funds made it possible for military HIV researchers to focus attention on unique problems of infected women.

As an example of practical but trivialized and overlooked needs, women have special challenges in field environments where personal hygiene may be difficult to manage. Human fungal infections, including vaginal yeast infections, may be difficult to treat, especially as resistant strains begin to appear. A series of laboratory studies led to the characterization and sequencing of a gene that is expected to provide an effective new drug target.[102,103] Several smaller studies advanced research on related topics, such as toxic shock,[104] *Mycoplasma* infection in women,[105] and hepatitis C infection in military women.[106]

Methods to improve screening tests in military clinical laboratories were also examined in DWHRP. A study of a new automated Pap-smear screening (PAPNET) showed that manual screen-

ing took three times longer than PAPNET-assisted rescreening. However, there was no benefit gained from the use of the expensive PAPNET system.[107] PAPNET was not cost-effective in this strategy, and the resources saved could be better invested in more effective screening. Increasing the number of women screened rather than computer-assisted rescreening would be a more effective cervical cancer mortality prevention. The authors concluded that these resources could be more effectively spent on education efforts to improve sampling techniques.[107]

Methods to translate research findings into knowledge that can be made immediately useful to women were pioneered in the DWHRP. A new concept of knowledge management based on fuzzy logic associations and filtering was developed to give women access to precise and reliable health information.[108,109] This started as part of a pilot project to provide up-to-date information automatically through the Defense Women's Health Research Clearing House, which later evolved into a national women's health website operated by Health and Human Services (*www.WomensHealth.gov*). One demonstration of the concept was the DoD Defense Breast Cancer Decision Guide. Because of the broader applications of this invention, this was recognized by a Smithsonian-Computerworld Innovation award and accepted into the Smithsonian Institution's Permanent Research Collection of Information Technology. The actual system was not continued beyond the life of DWHRP research funds.

SOCIOCULTURAL INFLUENCES OF MILITARY LIFE ON HEALTH

Work environment and coping

Psychological stress in the military environment has a variety of important effects, ranging from health risk behaviors and perceptions of well-being to effects on unit cohesion and readiness. The DWHRP supported the first look at responses of servicewomen in the 1995 DoD Survey of Health-Related Behaviors Among Military Personnel. Previously, data from these periodic surveys had always been lumped together without consideration of gender, or female responses had been ignored. In this analysis, family and workplace issues were important sources of stress cited by men and women alike.[110] The majority of servicewomen, however, also cited stress associated simply with being a woman in the predominantly male workforce,[110] adding one more factor to the total stress load of these service members. Self-reported coping behaviors differed between military men and women. Based on data from the 1995 DoD survey, nearly 90% of women worked on problem solving and talked to friends, but 60% reported that they also exercised or ate, 24% had a cigarette, and 17% had a drink in response to psychological stress.[90] Although smoking appears to be an important coping mechanism in military women, alcohol use was specifically affected by stressors, such as deployment[111] (Fig. 12). Heavy alcohol use in recently deployed women (12%) was half that of men (24%), but this was three times higher than in nondeployed women.[111] Similar data were reported for alcohol use in women assigned to Korea (18%, vs. 36% for men) compared with women assigned to Fort Lewis, Washington (9%).[112] The high rates of nicotine addiction noted in the Navy POWR study were also associated with greater risk of alcohol abuse; women who were hardcore smokers had a three-fold greater history of trauma or abuse, suggesting that cigarettes either are a coping strategy or indicate risk taking.[91]

Stress associated with deployments appeared to increase healthcare-seeking behavior and possibly influenced differences in health status. Women veterans in the Fort Devens cohort study were more likely than men to report chronic multisymptom illnesses following the Gulf War deployment.[113] Healthcare use tends to be higher in women than men, and the factors that further modify this have not been thoroughly explored. A comparison of soldiers assigned to units in Korea and Washington State suggested a poorer perception of personal mental health and indicated 10% more clinic visits by female soldiers in Korea compared with those at Fort Lewis. However, other indicators did not suggest differences in physical health status.[112] Preliminary analyses of these data suggested several factors associated with these differences in healthcare use, including family separation, assignment preference, and alcohol use.[112] In more specialized settings, this may be quite different. For example, male Air Force pilots were more stressed about family issues than female pilots, who were more likely to be deferring their family plans and did not have the same issues.[40]

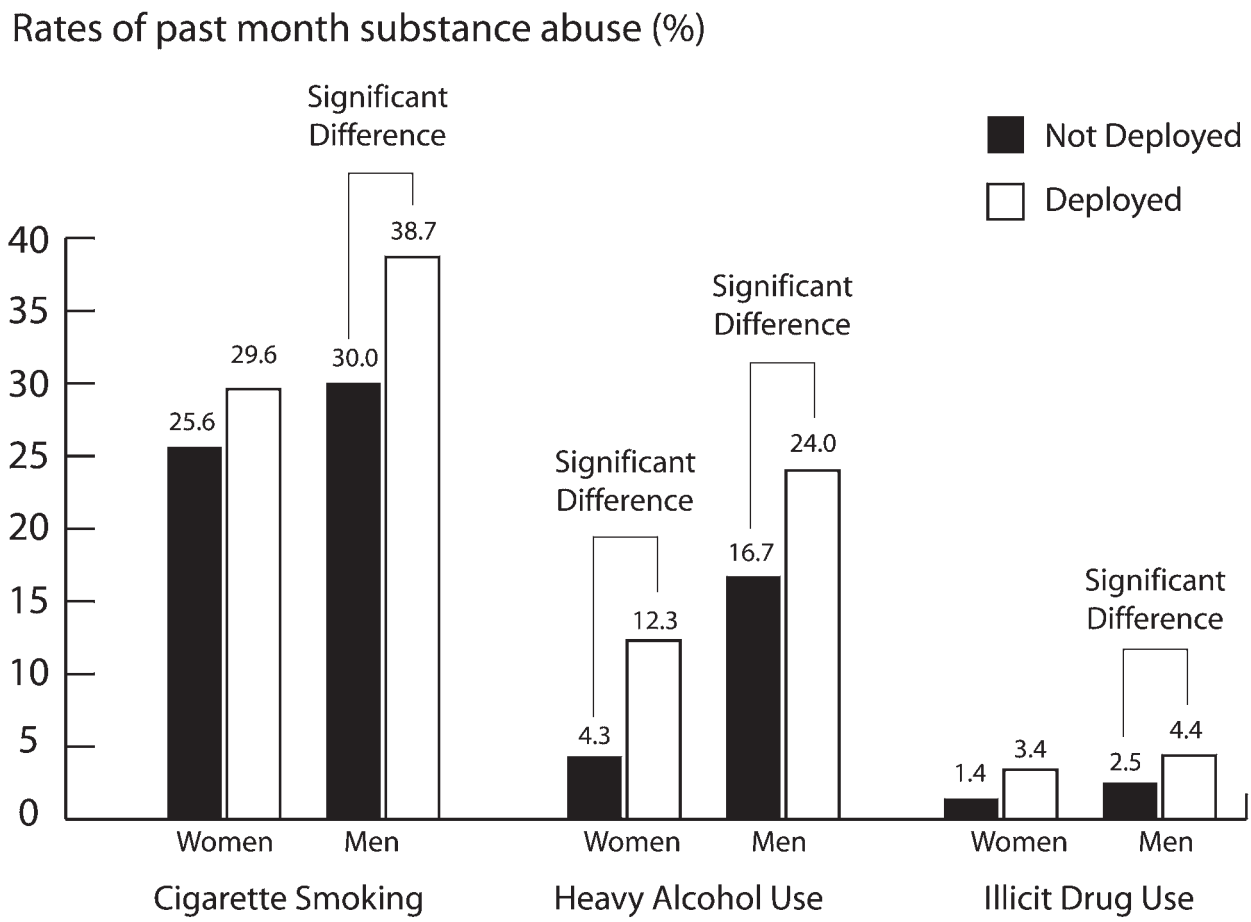

FIG. 12. Rates of past month substance use by deployment status of military men and women based on data from the 1995 DoD Survey of Health Related Behaviors Among Military Personnel. Smoking rates were high in military women (with overall rates of 26.3%, compared with 32.7% for men) and relatively unaffected by deployment stressors. Heavy alcohol use was relatively low in military women (5.3%, compared with 18.8% in military men) but significantly higher in recently deployed women.[111]

Pregnancy timing has a major impact on work climate, including perceptions of nondeployables due to pregnancies and dependent care concerns. A detailed study of pregnancy in the workplace recommended that some of the observed problems could be mitigated with "more training about pregnancy policy to improve understanding of how the organization intends to treat pregnant personnel in the workplace and to understand health care and employment benefits."[53,114] Another part of the solution is better training and access to preventive medicine services for the most junior enlisted servicewomen. This includes the type of effective skills training that was developed for new recruits on unintended pregnancy and STD prevention,[70] but there is also a need for gynecological services and advice, free of typical barriers associated with a sick-call request, including privacy issues and convenient access. A consistent finding in independent DWHRP studies was that unplanned pregnancies were most prevalent in the youngest and lowest-ranking servicewomen, and this group was more likely to have pregnancy complications.[56,57]

Sexual harassment and assault

In combat support units at three Army posts, 30% of the women and 8% of the men reported being sexually harassed in the previous year.[115] In a survey of Air Force women, more than half of the women reported sexual harassment during their time in the military.[116] In a survey of women extending back to the Vietnam era, 79% reported sexual harassment during their military careers, and over half (54%) had unwanted sex-

ual contact. Sexual harassment was generally related to poor leadership and hostile work environments[117–119] and to male soldiers' lack of acceptance of women as fellow soldiers.[120] Sexual harassment also reportedly degraded unit readiness, including the psychological well-being of men in problem units, and predicted a greater wish among the men in those units to leave the Army.[120] There was initial resistance within members of several services even to allow these studies to proceed on the stated basis that discovering a high prevalence would not solve a problem and could only discredit the military. This further highlighted the need for these studies, which demonstrated the importance of leadership action and intervention.[117–119] These studies each had their own definitions of sexual harassment, but it is likely that virtually every military woman has, at some point in her career, encountered harassment that affected work performance.

Half of servicewomen typically reported some kind of premilitary sexual or physical abuse, but women across studies also reported high rates of assault during their time in the military. One of the important findings from DWHRP research was the demonstration of poorer health status (including posttraumatic stress disorder [PTSD]) of women with a history of sexual assault regardless of when it occurred[116,121,122] (Fig. 13). In a stratified telephone survey of 537 female veterans from Vietnam to the present era (respondents from 2172 women in a random sample), 48% experienced violence during military service, including rape (30%), physical assault (35%), or both (16%); and these women were more likely to report chronic health problems, including prescription medication use for emotional problems. Assaulted or raped women reported significantly lower health-related quality of life and health impairments, comparable to women with chronic illnesses.[122,123] In another study, over half (51%) of current female soldiers studied reported being sexually assaulted, including rape (22.6%), although the majority of sexual assaults occurred before entering the military.[118] In an Air Force study, lifetime prevalence of rape was more than double national rates, using the same measures.[116] The data from these studies also suggested that prior history of assault may somehow differentially expose soldiers to sexual assaults in the military.[116,124,125] Another study suggested that such individuals could be identified and targeted for early coping skills development within their basic training course.[126]

There were several important findings from these studies. The high prevalence of lifetime abuse of military women is significant for military readiness because of the effect on health and attrition. This might be effectively addressed in initial entry training through programs to build coping skills. The continuing problem of sexual harassment and violence in the military needs to be addressed through a zero tolerance policy and more effective leadership training and emphasis, as well as early indoctrination in consideration of

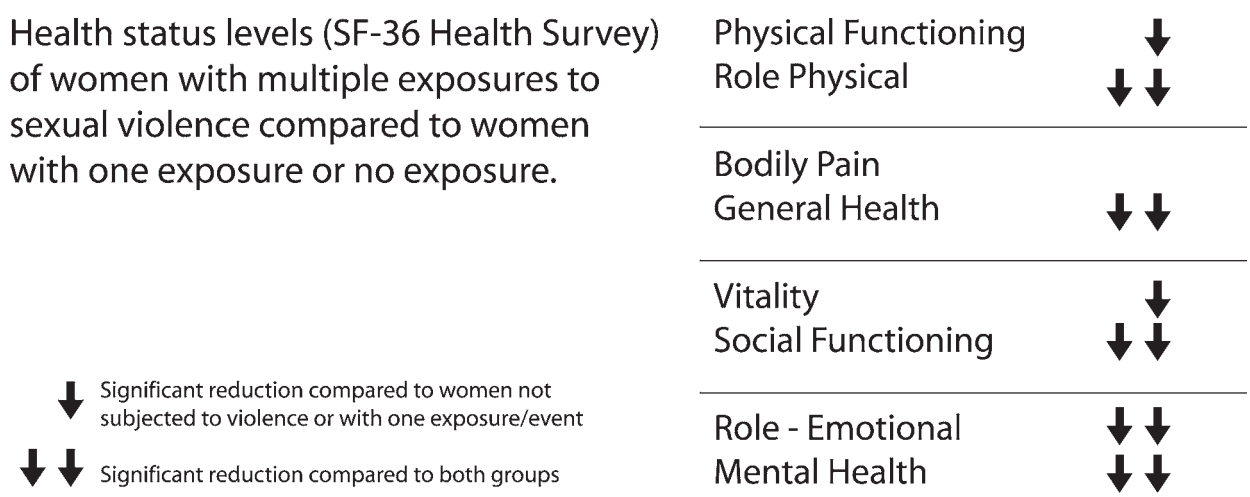

FIG. 13. Health status levels (based on the Short Form-36) of women with multiple exposures to sexual violence compared with women with one exposure and no exposure (two arrows = significantly lower compared with both other groups; one arrow = significantly lower compared with one other group).[122] This highlights the substantial health impact of sexual trauma.

others and team building for young male and female recruits.

PROTECTION OF WOMEN'S PERFORMANCE IN EXTREME OPERATIONAL ENVIRONMENTS

Altitude and progestogen benefits

It had been postulated that women in their luteal phase would perform better following rapid ascent to high altitude and might also suffer a lower incidence of acute mountain sickness. This was based on the observations of the effects of pharmacological doses of progestogens on chemoreceptor sensitivity in the brain. Laboratory and field DWHRP studies provided resoundingly negative data, even with 20-fold changes in circulating progesterone levels between early follicular and midluteal menstrual phases.[127] Ventilatory drives did not change across menstrual phase and were not different from those of men ascending to altitude.[128] Neither maximal nor submaximal exercise performance was altered across menstrual phase at altitude.[129] Red blood cell production at altitude was also not influenced by menstrual phase.[130] Energy requirements and fuel metabolism were similar to those of men, with an increased energy requirement in the first few days at altitude,[131] but women had a lower reliance on carbohydrate metabolism at altitude, possibly related to sympathetic responses.[132–134] At sea level and altitude, women exhibited slower fatigue and faster recovery from small muscle exercise than men.[135,136] Thus, despite decades of learned opinions on the existence of gender differences at altitude, these extensive studies indicated that women were neither handicapped nor advantaged at altitude by ovarian hormones or by their normal fluctuations.[127] Women may have an advantage over men with regard to small muscle performance.[135,136]

Gender differences in thermal strain

Progesterone raises core body temperature, with a mean temperature rise in the luteal phase (about 0.3°–0.5°C) that was shown to be equivalent to the fluctuations observed in circadian timing, heat acclimation, exercise training, and dehydration. However, this change in mean temperature between the early follicular and midluteal phases was additional to these other factors.[137] It was also demonstrated that peripheral blood flow increases in response to heat load during exercise were higher in the luteal phase[138] (Fig. 14). Although seemingly trivial, these menstrual cycle differences were important considerations in development and validation of physio-

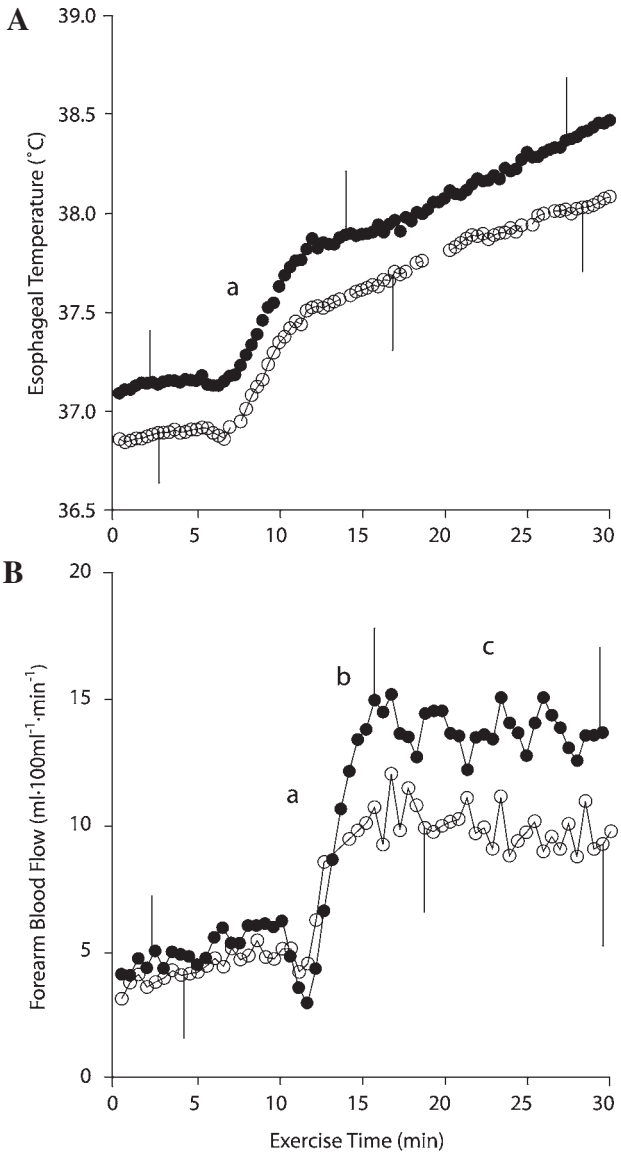

FIG. 14. Mean changes in core temperature and forearm blood flow during exercise by women in luteal (empty circles) and early follicular phase (open circles) of the menstrual cycle (reproduced with permission from ref. 138). The top chart shows changes in core body temperature, and the bottom chart depicts changes in forearm blood flow in the same experiments. Vertical lines indicate standard deviations; letters designate (**a**) the exercise transient, (**b**) attenuation of the increase in forearm blood flow, and (**c**) the leveling off of forearm blood flow at two different levels depending on the phase of the menstrual cycle.

logical models that predict responses to exercise and heat and cold exposures[138–142] (Fig. 15).

A suspected gender difference in exertional heat illness (EHI) was investigated in a joint effort between Army and Navy investigators studying Marine Corps recruits during summer training in North Carolina. A retrospective analysis of 10 years of data had previously identified comparable rates of EHI in female recruits (11% of all EHI patients; 10% of trainees were female) but a marked difference in EHI hospitalization (11% of male and no female EHI patients). It was suggested that this lower rate of severity in women might reflect a more fundamental difference in the pathophysiology of EHI in women because of other differences in the presentation of cases (e.g., mean peak temperature for nonhospitalized women was lower than for the men, but enzyme levels reflecting cellular damage were higher in the women). Reanalysis of these earlier data produced recommendations for safer hot weather training for men and women, based on a finding that cumulative (previous day) heat exposure increases risk of EHI.[143] The DWHRP study attempted to resolve the possible role of heat shock resistance in EHI cases but concluded from lymphocyte responses that there were no qualitative differences between individuals exercising, heat exposed, and with EHI, with differences only in the severity of the response.[144] In a separate study, estrogen supplementation to young women did not alter exercise-induced heat shock protein responses in leukocytes or thermosensitivity, including threshold of sweating, peripheral blood flow, and protective biochemical responses.[145]

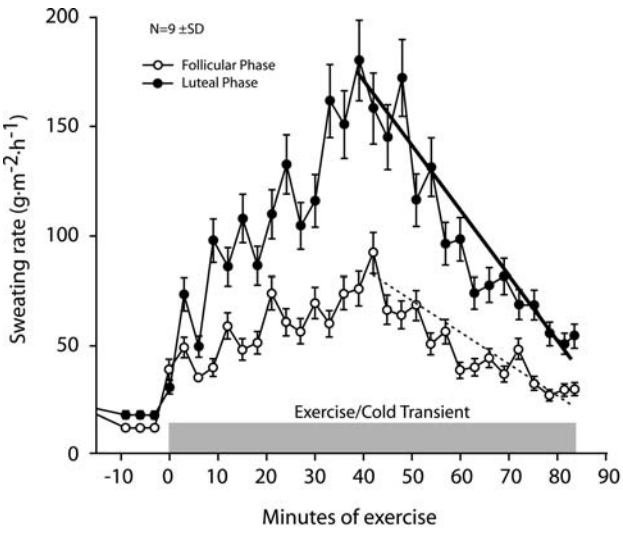

FIG. 15. The effect of menstrual phase on sweat rate during exercise with cold exposure, demonstrating a faster rise in sweat rate during the luteal phase (until inhibition occurs in response to cooling of skin temperature) (reproduced with permission from ref. 141). These data show the small but important effect of menstrual cyclicity on thermoregulatory responses that must be considered in predictive physiological models.

Cold strain and physiological responses changed in the luteal phase compared with the early follicular phase in a study that also compared light clothing and full uniforms.[146] In this study, particularly for the light clothing arm of the experiment, the onset of shivering was delayed in the luteal phase, and cold tolerance was extended for women briefly exposed to an average −5°C air temperature. These data suggested that a warmer central core produced this greater tolerance time in the luteal phase.[146] Another project with a different testing approach challenged central responses at a constant skin temperature using occlusion of peripheral blood flow; these studies failed to identify differences in core thermosensitivity across menstrual cycle phases with cold air and cold water immersion exposure conditions.[147,148] There were also no important differences between men and women in the measured cold responses, except for greater heat production rates in the men.[147,148]

The extensive DWHRP studies on heat, cold, and altitude exposures found fewer differences across menstrual cycles or between men and women than had been originally predicted or assumed. In physiological studies of tightly controlled effector responses involving both male and female subjects, variability can be reduced by studying the women in the early follicular phase of their menstrual cycle. In extreme environments, menstrual cycle changes do not appear to have any major effects on responses that would substantively affect the health and performance of women.

Voluntary dehydration

Military research over many years has clearly defined the importance of adequate water intake to prevent performance decrements and heat injury. Deliberate water restriction by women emerged as potentially serious concerns in several DWHRP studies. One third of 450 female soldiers surveyed indicated that they had experienced urinary incontinence problems during exercise and field training, 20% stated that they

had leaked significantly during the Army Physical Fitness test, and 30% took precautions to avoid embarrassing themselves during physical training, including restricting water intake; 12% of women dropping out of airborne training cited urinary incontinence as a major factor in their decision; and 5% felt that their urine leakage had a significant impact on their regular duties.[149,150] Women were shown to have higher rates of excretion of a water load compared with men.[151] At least 10% of the women indicated that they restricted fluid before physical training and while participating in field exercises.[149,150] Kegel exercises, with and without biofeedback, provided significant benefits, with both groups being able to prevent episodes of incontinence.[152] A major remaining challenge is getting the treatment to Soldiers through education programs, including Kegel clinics.[152] Two other studies provided favorable evaluations of commercial devices to enable women to urinate in space-limited crew compartments (e.g., airplane cockpits) and in the field. Dehydration remains an important problem for military women. Significant assistance may come from the development of a hydration monitor as part of current physiological monitoring research efforts.

Pharmacological performance enhancement

Most of the work on performance-enhancing drugs has been conducted by the military, and nearly all of this research has been conducted on males. Interactions of bright light and caffeine were found to produce effects similar to those observed for men on physiological sleep parameters (melatonin and temperature changes), and there were no important effects across menstrual phase.[153] On the other hand, sleep deprivation affected cognitive deficits and alertness less in women than in men when the women were tested in their luteal phase.[154] Melatonin was tested at the highest doses (10 mg/day) contemplated for resynchronization of human performance cycles in travel across multiple time zones. The goal was to determine if this potential intervention would affect ovarian function. No adverse effects were observed on pituitary hormone secretion, and performance was generally improved by melatonin in an 8-hour time zone shift, although some cognitive tests demonstrated degradation of performance.[155] In a serendipitous observation, the hormone appeared to produce some specific perceived benefits in mood.[156] A study of the effects of caffeine on 3-hour vigilance performance showed that 200 mg did not harm marksmanship performance and abolished the deterioration normally observed with time on sentry duty.[157] Amphetamines, well tested in male soldiers in the 1940s for performance enhancement, worked equally well in female aviators to sustain performance in a flight simulator after 40 hours of sleep deprivation.[158] All these drug studies provided evidence that the fatigue countermeasures under consideration were likely to be as safe and effective for women as for men.

Gender differences in decompression sickness

Aviators exposed to high altitude (e.g., 35,000 feet) for more than 30 minutes are at greatly increased risk for altitude decompression sickness (DCS). This is similar to the bends that occur when Navy divers go from higher pressure undersea environments back to sea level and nitrogen escapes into the system, forming bubbles that can cause serious pain and injury. Based on reviews of early data on women during altitude chamber training, there was a perception that women were at greater risk for DCS than men, reinforced by the theoretical association expected from gender-specific, higher relative body fat (where nitrogen is dissolved). In a series of 25 altitude chamber decompression studies, nearly 100 women were studied alongside men for 961 exposures to simulated altitude for up to 8 hours using 0–4 hours of preoxygenation. There was no significant difference in the incidence of DCS observed (50% of males and 45% of females), but contrary to expectations, significantly more men demonstrated venous gas emboli.[159] These data clearly indicate that women are at no greater risk for DCS than men, and they may be less susceptible.

G-force protection

Similar anecdotal data and assumptions suggested that women were less able to tolerate G-forces in a centrifuge, with rationalizations that women could not create as much muscular force to counter the G-forces. Anti-G-suit modifications that improved the fit to accommodate female anthropometry, including keeping the suit below the ribcage, nearly doubled the endurance time for women and abolished any gender differences

in performance[160] (Fig. 16). Another study considered neuropsychological performance after 24 hours of sleep deprivation and after 2 or 4 weeks of layoff (deconditioning) and found no important differences between men and women. Physiological measures indicated better G-tolerance of women, but this was not matched by better performance.[161] These studies indicate that women can manage G-forces as well as men.

FUTURE DIRECTIONS

The DWHRP provided opportunities to rapidly narrow knowledge gaps on issues of potential importance to military women (Table 5). In many cases, research efforts already underway and with clear and well-developed questions were provided the organizational and financial push needed to complete important projects. Other projects explored uncharted territory and evolved new and important questions, some of which have been further addressed through other programs (Table 1). Even within the first year of DWHRP execution, research priorities began to shuffle. Some issues quickly emerged as not having any important gender bias, driven by long-standing myth, or even motivated by researchers and organizations that simply wanted continued funding. Other problems were solved, confirming that capable and competent researchers can declare victory in a topic and move to new research questions (Table 3).

Several issues have moved to the top of the list of unanswered questions that are uniquely important to the health and performance of military women. Based on what has been accomplished and questions and problems that continue to surface, the big five biomedical research gaps for military women are military families, physical training injuries, mental health and psychological resilience, reproductive hazards in the workplace, and healthcare delivery (Table 6). In the past decade, long-term health outcomes have be-

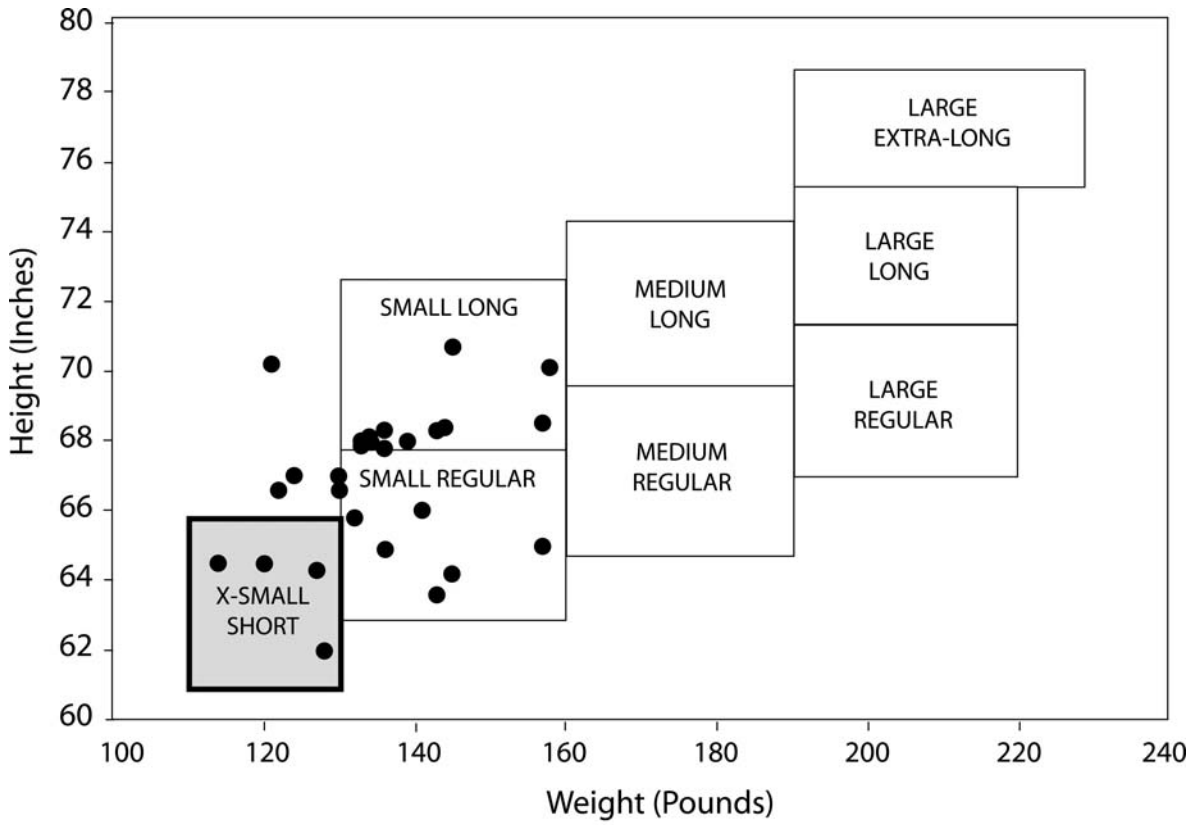

FIG. 16. Height and weight of 28 female pilots superimposed over area blocks representing seven standard sizes and the new x-small short size of the CSU-13B/P anti-G suit (reproduced with permission from ref. 160). These data highlight the need for this additional size to properly protect normal female pilots. The study demonstrated that women could tolerate G-forces at least as well as men when provided with properly fitted G-suits.

TABLE 5. REVISED PHYSIOLOGICAL CONCEPTS BASED ON FINDINGS FROM THE DWHRP PROJECTS

Generally accepted concept or physiological knowledge gap	*Conclusive discovery and revised physiological concept*	*Key references*
Unknown: physical strength trainability of women	Specificity of training was demonstrated with increases in upper and lower body strength measures	9,10,13
Bone mineral density is a primary determinant of stress fracture	Bone geometry is particularly important to prediction of risk of stress fracture and may be more important than bone density	26
Increased risk of menstrual disturbances and bone loss from high volume exercise (female athlete triad)	Exercise does not affect LH pulsatility in healthy young women if energy requirements are met	45
Unknown: time course of body composition and fitness return to prepregnancy levels	Women with normal gestational weight gain do not typically return to nonpregnancy weights and physical fitness before 6 months postpartum	47,48,50, 51
Unknown: pathophysiology of maternal malaria	Primiparous women lacking antiadhesion protein antibodies are at greater risk for placental invasion of malaria parasites of a wide range of strains	75,76,77
Enhanced performance at altitude during luteal phase	Progesterone increases in the luteal phase provide no special benefits to performance or reduced incidence of acute mountain sickness	129
Protective effect of estrogen in heat injury	Estrogen provides no apparent advantage in heat tolerance, and differences in hospitalization rates remain to be explained	143,145
Greater risk of decompression sickness	Women have no greater incidence of decompression sickness than men and may actually have a reduced frequency of bubble formation	159
Poorer tolerance of G-forces	When provided with G-suits that fit, women tolerate G-forces as well as men	160

come an important topic of medical research for the DoD because of increasing public expectations of health protection and well-being of all service members. Postdeployment and service-related health problems were not previously a focus of DoD research, nor was there much attention to issues of wellness or the larger context of soldier families and psychosocial influences. Today, many of these issues are command priorities and are encompassed in new regulations and policies.

Additional research to enhance protection of long-term health is the focus of a major initiative in Force Health Protection that grew out of studies on Gulf War illnesses, and this and related initiatives cover some of the significant remaining research gaps of importance to the health and performance of military women. This includes collaborative efforts by the Army and the Department of Veterans Affairs on psychological health of service members involved in current deployments to Iraq and Afghanistan, including the important role of military families in individual resilience and investigation of potential gender differences in the effects of traumatic exposures. With the rapid mobilization of older age reserve forces, new concerns about physical training injuries are being addressed as part of a major Army and DoD research initiative, with a series of studies on scientifically based training programs that produce training benefits with fewer injuries, exploration of injury markers, and continued work on improvement of bone health and stress fracture prevention. Many field healthcare delivery problems that were identified as special issues for women in the Gulf War deployment in 1991 have been fixed or are being further improved through investigation of new advanced diagnostic and treatment technologies. The Tri-Service Nursing Research Program has produced several important assessments of womens' field hygiene and health care practices and needs. Reproductive hazards have been investigated through the newly established DoD Birth Defects Registry and are part of the research objectives of the Millenium Cohort Study, a 22-year

Table 6. Priorities for Additional Research of Special Importance to Health of Military Women

Devise psychological support strategies for military families and service members, including deployed mothers and dual-service couples
Solve the problem of high rates of musculoskeletal injuries, including those related to physical training, occupational strength requirements, and bone health
Determine if neuropsychological responses to traumatic events (e.g., PTSD) occur with greater prevalence in women or have different clinical presentations affecting diagnosis and treatment
Investigate mechanisms of reproductive hazards, including common military exposures that may affect fertility of a young woman or lead to long-range consequences for an exposed fetus
Fix deficiencies in clinical care needs specific to women in garrison and in the field, providing supplies and treatments for gynecological health and birth control and further developing field medical treatment technologies

prospective health outcomes study involving over 100,000 service members, including an oversampling of military women (25%).

Women probably should not be singled out with another version of the special congressional appropriation (DWHRP); instead, relevant topics can be identified as priorities within core research budgets in the DoD and addressed through DoD laboratory collaborations with extramural capabilities and expertise. In addition to this programmed funding, congressionally directed funds focused on solving specific problems that would otherwise remain underfunded in any national agency agenda (e.g., stress fracture) continue to help advance medical research with specific benefits to women. There is also a need to expand DoD research to more translational efforts that concentrate on turning knowledge into scientifically based policies and programs, including rigorous cost-benefit analyses and randomized controlled trials, such as the DWHRP projects on *Chlamydia* management[66,67] and the training program for unintended pregnancy and STD prevention.[70] The success of those projects demonstrate the value of committing large costs to properly designed and powered studies that will provide definitive answers instead of conducting smaller and repeatedly ineffectual efforts that still cost the taxpayer but never produce new or effective solutions.

The flurry of interest stimulated by the large bolus of funding for military women's research created a long-lasting awareness that the DoD is interested in providing the best possible health protection and performance enhancement for military women. It also increased visibility of many interesting and unanswered questions for the wider research community to address.

ACKNOWLEDGMENTS

Three individuals made the DWHRP possible: COL Fred Tyner (Acting Commander, USAMRDC), LTC Mary Z. Mays (Chief, Programs, USAMRDC), and COL James Martin (Pentagon liaison for USAMRDC). The service representatives that further guided the program were COL Robert Gifford (USAMRDC), CAPT Robert Carter (BUMED), and Lt. Col. Dan Brown (AFMOA). LTC Kathryn Knudsen was invaluable in the early days of setting up the program and drew on her experience with management of a previous related effort on military women's research. Dr. Gillian Woollett (American Institute of Biological Sciences) thoughtfully planned and conducted the peer review of the extramural program proposals, recruiting the many national experts who participated in the peer review and helped inspire the DoD to develop more than just another research funding opportunity. A dedicated staff at USAMRMC (previously USAMRDC) kept track of the program for the past decade, including Ms. Judy Pawlus (reports management), Ms. Pat Fritz (contracting), Ms. Ellen Santaliz (accounting), and especially Ms. Buffy Burdette (overall administration for the life of the program). Figures in this report were produced by Mr. Philip Fujawa.

REFERENCES

1. Santee WR, Kraning KK, Matthew WT. Modeling analysis of women litter bearers during heat stress. Aviat Space Environ Med 1999;70:340.
2. Harper WH, Knapik J, dePontbriand R. Female load-carrying performance. Technical Report ARL-TR-1176. Aberdeen Proving Ground, MD: Army Research Laboratory, March 1997. AD-A323 483.
3. Baisden AG, Pokorski TL, Meyer SG. Development of gender-neutral occupational standards. II. Job demands and physiological issues regarding female combat pilots. SAFE J 1995;25:22.

4. Morris CE, Popper SE. Gender and effect of impact acceleration on neck motion. Aviat Space Environ Med 1999;70:851.
5. Marras WS, Davis KG, Jorgensen MJ. Spine loading as a function of gender. Spine 2002;27:2514.
6. Marras WS, Jorgensen MJ, Granata KP, Wiand B. Female and male trunk geometry: Size and prediction of the spine loading trunk muscles derived from MRI. Clin Biomech 2001;16:38.
7. Amoroso PJ, Yore MM, Smith GS, Lopez M. Analysis of military occupational specialties and hospitalization. Part 1: 25 largest Army enlisted occupations. Technical Report T98-7. Natick, MA: U.S. Army Research Institute of Environmental Medicine, November 1997. AD-A332904.
8. Lincoln AE, Smith GS, Amoroso PJ, Bell NS. The natural history and risk factors of musculoskeletal conditions resulting in disability among U.S. Army personnel. Work 2002;18:99.
9. Knapik JJ. The influence of physical fitness training on the manual material handling capability of women. Appl Ergonomics 1997;28:339.
10. Harman E, Frykman P, Palmer C, Lammi E, Reynolds K, Backus V. Effects of a specifically designed physical conditioning program on the load carriage and lifting performance of female soldiers. Technical Report T98-24. Natick, MA: U.S. Army Research Institute of Environmental Medicine, November 1997. AD-A330237.
11. Reynolds KL, Harman EA, Worsham RE, Sykes MB, Frykman PN, Backus VL. Injuries in women associated with a periodized strength training and running program. J Strength Cond Res 2001;15:136.
12. Nindl BC, Harman EA, Marx JO, et al. Regional body composition changes in women after 6 months of periodized physical training. J Appl Physiol 2000;88: 2251.
13. Kraemer WJ, Mazzetti SA, Nindl BC, et al. Effect of resistance training on women's strength/power and occupational performances. Med Sci Sports Exerc 2001;33:1011.
14. Kraemer WJ, Nindl BC, Ratmess NA, et al. Changes in muscle hypertrophy in women with periodized resistance training. Med Sci Sports Exerc 2004;36:697.
15. Nindl BC, Kraemer WJ, Gotshalk LA, et al. The effects of resistance training on augmenting women's performance during a high-intensity military relevant manual materials handling task. In: Kumar S, ed. Advances in occupational ergonomics and safety. Amsterdam, The Netherlands: IOS Press, 1998:723.
16. Kraemer WJ, Nindl BC, Gotshalk LA, et al. Hypertrophy of the upper and lower body musculature in women following 6 months of periodized heavy resistance training. In: Hakkinen K, ed. International Conference on Weightlifting and Strength Training. Jyvaskyla, Finland: Gummerus Printing, 1998:171.
17. Robinson MD. Muscle activity and fatigue during push-ups performed by women: An electromyographic and videographic analysis of fifteen muscles. Final Report. Washington D.C.: Walter Reed Army Medical Center, April 1996. AD-A328281.
18. Boyea SR. Pushup performance by women: Analysis of modes of failure. Final Report. Washington, DC: Walter Reed Army Medical Center, October 1995. 95MM5538.
19. Shaffer RA, Brodine SK, Ito SI, Le AT. Epidemiology of illness and injury among U.S. Navy and Marine Corps female training populations. Mil Med 1999; 164:17.
20. Snedecor MR, Boudreau CF, Ellis BE, Schulman J, Hite M, Chambers B. U.S. Air Force recruit injury and health study. Am J Prev Med 2000;18(3 Suppl): 129.
21. Bell NS, Mangione TW, Hemenway D, Amoroso PJ, Jones BH. High injury rates among female Army trainees—A function of gender? Am J Prev Med 2000;18(Suppl):141.
22. Almeida SA, Trone DW, Leone DM, Shaffer RA, Patheal SL, Long K. Gender differences in musculoskeletal rates: A function of symptom reporting? Med Sci Sports Exerc 1999;31:1807.
23. Lappe JM, Stegman MR, Recker RR. The impact of lifestyle factors on stress fractures in female Army recruits. Osteoporos Int 2001;12:35.
24. Committee on Body Composition, Nutrition, and Health of Military Women. Committee on Military Nutrition Research. Food and Nutrition Board. Institute of Medicine. Reducing stress fracture in physically active military women. Washington, DC: National Academy Press, 1998.
25. Kelly EW, Jonson SR, Cohen ME, Shaffer R. Stress fractures of the pelvis in female Navy recruits: An analysis of possible mechanisms of injury. Mil Med 2000;165:142.
26. Beck, TJ, Ruff CB, Shaffer RA, Betsinger K, Trone DW, Brodine SK. Stress fracture in military recruits: Gender differences in muscle and bone susceptibility factors. Bone 2000;27:437.
27. McDermott MT, Christensen RS, Lattimer J. The effects of region-specific resistance and aerobic exercises on bone mineral density in premenopausal women. Mil Med 2001;166:318.
28. Garland FC. Hospitalization rates for military women: Feasibility and design of a tri-service relational database architecture allowing service-specific and tri-service reporting. Final Report. San Diego, CA: Naval Health Research Center, January 1996. 95MM5523.
29. Garland FC. Women aboard Navy ships: A comprehensive health and readiness research project. Final Report. San Diego, CA: Naval Health Research Center, March 1996. 95MM5522.
30. Lincoln AE, Smith GS, Baker SP. The use of existing military administrative and health databases for injury research. Am J Prev Med 2000;18:8.
31. Bell NS, Amoroso PJ, Yore MM, Smith GS, Jones BH. Self-reported risk-taking behaviors and hospitalization for motor vehicle injury among active duty Army. Am J Prev Med 2000;18:85.

32. Amoroso PJ, Smith GS, Bell NS. Qualitative assessment of cause-of-injury coding in military hospitals: NATO Standardization Agreement (STANAG) 2050. Am J Prev Med 2000;18:174.
33. Amoroso PJ, Bell NS, Smith GS, Senier L, Pickett D. Viewpoint: A comparison of cause-of-injury coding in U.S. military and civilian hospitals. Am J Prev Med 2000;18:164.
34. Amoroso PJ, Bell NS, Jones BH. Injury among female and male Army parachutists. Aviat Space Environ Med 1997;68:1006.
35. Smith GS, Dannenberg AL, Amoroso PJ. Hospitalization due to injuries in the military—Evaluation of current data and recommendations on their use for injury prevention. Am J Prev Med 2000;18(Suppl):41.
36. Lauder TD, Baker SP, Smith GS, Lincoln AE. Sports and physical training injury in hospitalizations in the Army. Am J Prev Med 2000;18:118.
37. Sulsky SK, Mundt KA, Bigelow C, Amoroso PJ. Risk factors for occupational knee-related disability among enlisted women in the U.S. Army. Occup Environ Med 2002;59:601.
38. Lincoln AE, Vernick JS, Ogaitis S, Smith GS, Mitchell CS, Agnew J. Interventions for the primary prevention of work-related carpal tunnel syndrome. Am J Prev Med 2000;18(Suppl 4):37.
39. Wong TY, Smith GS, Lincoln AE, Teilsch J. Ocular trauma in the United States Army: Hospitalization records from 1985 through 1994. Am J Ophthalmol 2000;129:645.
40. McGlohn SE, King RE, Butler JW, Retzlaff PD. Female United States Air Force (USAF) pilots: Themes, challenges, and possible solutions. Aviat Space Environ Med 1997;68:132.
41. Committee on Body Composition, Nutrition, and Health of Military Women. Committee on Military Nutrition Research. Food and Nutrition Board. Institute of Medicine. Assessing readiness in military women—The relationship of body composition, nutrition, and health. Washington, DC: National Academy Press, 1998.
42. Cline AD, Patton JF, Tharion WJ, et al. Assessment of the relationship between iron status, dietary intake, performance, and mood state of female Army officers in a basic training population. Technical Report T98-24. Natick, MA: U.S. Army Research Institute of Environmental Medicine, September 1998. AD-A351973.
43. Committee on Military Nutrition Research. Food and Nutrition Board. Institute of Medicine. A review of issues related to iron status in women during U.S. Army Basic Combat Training. Letter Report to BG Russ Zajtchuk. Washington, DC: National Academy of Sciences, December 19, 1995.
44. Ihle R, Loucks AB. Dose-response relationships between energy availability and bone turnover in young exercising women. J Bone Min Res 2004;19: 1231.
45. Loucks AB, Thuma JR. Luteinizing hormone pulsatility is disrupted at a threshold of energy availability in regularly menstruating women. J Clin Endocrinol Metab 2003;88:297.
46. Young VR. Metabolic response to food restriction in military-eligible women with a gender comparison. Final Report. Cambridge, MA: Massachusetts Institute of Technology, October 1999. DAMD17-95-2-5015.
47. Butte NF, Ellis KJ, Wong WW, Hopkinson JM, Smith EO. Composition of gestational weight gain impacts maternal fat retention and infant birth weight. Am J Obstet Gynecol 2003;189:423.
48. Butte NF, Wong WW, Treuth MS, Ellis KJ, Smith EO. Energy requirements during pregnancy based on total energy expenditure and energy deposition. Am J Clin Nutr 2004;79:1078.
49. Butte NF, Treuth MS, Mehta NR, Wong WW, Hopkinson JM, Smith EO. Energy requirements of women of reproductive age. Am J Clin Nutr 2003;77: 630.
50. Treuth MS, Butte NF, Puyau M. Pregnancy-related changes in physical activity, fitness, and strength. Med Sci Sports Exerc 2005;37:832.
51. Dettori J, Westphal KA, Cline A, Pusateri A, Smith P, Patience TH. Support of USARIEM postpartum soldier research study. Final Report. Rockville, MD: Henry M. Jackson Foundation, September 1997. DAMD17-95-2-5016.
52. Altemus M, Redwine LS, Leong Y-M, Frye CA, Porges SW, Carter CS. Responses to laboratory psychosocial stress in postpartum women. Psychosom Med 2001;63:814.
53. Carter CS, Altemus M, Chrousos GP. Neuroendocrine and emotional changes in the postpartum period. Prog Brain Res 2001;133:241.
54. Carter CS. Neuroendocrine perspectives on social attachment and love. Psychoneuroendocrinology 1998;23:779.
55. Garland FC, Garland CF, Gorham ED. A model of the expected occurrence of adverse pregnancy outcomes aboard U.S. Navy ships. Mil Med 2000; 165:691.
56. Creedon J. Relationships between a female soldier's military occupational specialty (MOS) and birth outcome. Final Report. San Antonio, TX: Facilitators of Applied Clinical Trials, October 1996.
57. Evans MA, Rosen LN. Demographic and psychosocial risk factors for preterm delivery in an active duty pregnant population. Mil Med 2000;165:49.
58. Yen S, Shafer MA, Moncada J, Campbell CJ, Flinn SD, Boyer CB. Prevalence and clinical correlates of bacterial vaginosis among sexually experienced and non-sexually experienced young women entering the military. Obstet Gynecol 2003;102: 927.
59. Lu GC, Schwebke JR, Duffy LB, et al. Midtrimester vaginal *Mycoplasma genitalium* in women with subsequent spontaneous preterm birth. Am J Obstet Gynecol 2001;185:163.
60. Thomas MD, Thomas PJ, Garland FC. Contraceptive use and attitudes toward family planning in

Navy enlisted women and men. Mil Med 2001; 166:550.
61. Schwerin MJ, Sack DM. Shipboard women's health care: Provider perceptions. Mil Med 1997;162:666.
62. Thomas AG, Brodine SK, Shaffer R, et al. Chlamydial infection and unplanned pregnancy in women with ready access to health care. Obstet Gynecol 2001;98:1117.
63. Gaydos CA, Howell MR, Pare B, et al. *Chlamydia trachomatis* infections in female military recruits. N Engl J Med 1998;339:739.
64. Gaydos CA, Howell MR, Quinn TC, Gaydos JC, McKee KT. Use of ligase chain reaction with urine versus cervical culture for detection of *Chlamydia trachomatis* in an asymptomatic military population of pregnant and nonpregnant females attending Papanicolaou smear clinics. J Clin Microbiol 1998; 36:1300.
65. Kacena KA, Quinn SB, Howell MR, Madico GE, Quinn TC, Gaydos CA. Pooling urine samples for ligase chain reaction screening for genital *Chlamydia trachomatis* infection in asymptomatic women. J Clin Microbiol 1998;36:481.
66. Howell MR, McKee KT, Gaydos JC, Quinn TC, Gaydos CA. Point-of-entry screening for *C. trachomatis* in female Army recruits: Who derives the cost savings? Am J Prev Med 2000;19:160.
67. Howell MR, Gaydos JC, McKee KT, Quinn TC, Gaydos CA. Control of *Chlamydia trachomatis* infections in female Army recruits: Cost-effective screening and treatment in training cohorts to prevent pelvic inflammatory disease. Sex Transm Dis 1999;26:519.
68. Brodine SK, Shafer MA, Shaffer RA, et al. Asymptomatic sexually transmitted disease prevalence in four military populations: Applications of DNA amplification assays for *Chlamydia* and gonorrhea screening. J Infect Dis 1998;178:1202.
69. Shafer MA, Moncada J, Boyer CB, Betsinger K, Flinn SD, Schacter J. Comparing the FVU, self-collected vaginal swabs and endocervical specimens to detect *C. trachomatis* and *N. gonorrhoeae* using nucleic acid amplification tests. J Clin Microbiol 2003;41:4395.
70. Boyer CB, Shafer MA, Shaffer RA, et al. Evaluation of a cognitive-behavioral, group, randomized controlled intervention trial to prevent sexually transmitted infections and unintended pregnancies in young women. Prev Med 2005;40:420.
71. Smoak BL, Writer JV, Keep LW, Cowan J, Chantelois JL. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of U.S. Army servicewomen. J Infect Dis 1997;176:831.
72. Andersen SL, Oloo AJ, Gordon DM, et al. Successful double-blinded, randomized, placebo-controlled field trial of azithromycin and doxycycline as prophylaxis for malaria in western Kenya. Clin Infect Dis 1998;26:146.
73. Strickman D, Sheer T, Salata K, et al. *In vitro* effectiveness of azithromycin against doxycycline resistance and susceptible strains of *Rickettsia tsutsugamushi*, etiologic agent of scrub typhus. Antimicrob Agents Chemother 1995;39:2406.
74. Golenda CF, Solberg VB, Burge R, Gambel JM, Wirtz RA. Gender-related efficacy difference to an extended duration formulation of topical N, N-diethylm-toluamide (DEET). Am J Trop Med Hyg 1999; 60:654.
75. Fried M, Duffy PE. Adherence of *Plasmodium falciparum* to chondroitin sulfate A in the human placenta. Science 1996;272:1502.
76. Fried M, Duffy PE. Maternal malaria and parasite adhesion. J Mol Med 1998;76:162.
77. Fried M, Nosten F, Brockman A, Brabin BJ, Duffy PE. Maternal antibodies block malaria. Nature 1998; 395:851.
78. Fried M, Muga RO, Misore AO, Duffy PE. Malaria elicits type I cytokines in the human placenta: IFN-gamma and TNF-alpha associated with pregnancy outcomes. J Immunol 1998;160:2523.
79. Reutman SR, LeMasters GK, Knecht EA, et al. Evidence of reproductive endocrine effects in women with occupational fuel and solvent exposures. Environ Health Perspect 2002;110:805.
80. Puhala E, Lemasters G, Smith L, et al. Jet fuel exposure in the United States Air Force. Appl Occup Environ Hyg 1997;12:606.
81. Grajewski B, Waters MA, Whelan EA, Bloom TF. Radiation dose estimation for epidemiologic studies of flight attendants. Am J Indust Med 2002;41:27.
82. Whelan EA, Lawson CC, Grajewski B, et al. Prevalence of respiratory symptoms among female flight attendants and teachers. Occup Environ Med 2003; 60:929.
83. Grajewski B, Nguyen MM, Whelan EA, Cole RJ, Hein MJ. Measuring and identifying large-study metrics for circadian rhythm disruption in female flight attendants. Scand J Work Environ Health 2003; 29:337.
84. Whelan EA, Grajewski B, Wood E, et al. Feasibility issues in reproductive biomonitoring of female flight attendants and teachers. J Occup Environ Med 2002; 44:947.
85. Kritz-Silverstein D, Wingard DL, Garland FC. The association of behavior and lifestyle factors with menstrual symptoms. J Womens Health Gender-Based Med 1999;8:1185.
86. Deuster PA, Adera T, South-Paul J. Biological, social, and behavioral factors associated with premenstrual syndrome. Arch Fam Med 1999;8:122.
87. Young SA, Hurt PH, Benedek DM, Howard RS. Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: A randomized, double-blind, placebo-controlled crossover trial. J Clin Psychology 1998;59:76.
88. Ader DN, South-Paul J, Adera T, Deuster PA. Cyclical mastalgia: Prevalence and associated health and behavioral factors. J Psychosom Obstet Gynaecol 2001;22:71.
89. Euhus DM, Uyehara C. Influence of parenteral progesterones on the prevalence and severity of mastal-

gia in premenopausal women: A multi-institutional cross-sectional study. J Am Coll Surg 1997;184:596.
90. Bray RM, Fairbank JA, Marsden ME. Stress and substance use among military women and men. Am J Drug Alcohol Abuse 1999;25:239.
91. Hourani LL, Yuan H, Bray RM, Vincus AA. Psychosocial correlates of nicotine dependence among men and women in the U.S. naval services. Addict Behav 1999;24:521.
92. Weaver KB, Woodruff SI, Conway TL, Edwards CC, Zhu SH, Elder JP. Does the U.S. Navy attract young women who smoke? Occup Environ Med 1998; 55:792.
93. Edwards CC, Woodruff SI, Conway TL. Operation Stay Quit: Preventing smoking relapse among U.S. Navy women. Am J Health Behav 1999;23:352.
94. Woodruff SI, Conway TL, Edwards CC. Effect of an eight week smoking ban on women at U.S. Navy Recruit Training Command. Tobacco Control 2000;9:40.
95. Woodruff SI, Conway TL, Edwards CC. Increasing response rates to a smoking survey for U.S. Navy enlisted women. Eval Health Prof 2000;23:172.
96. Arsenault JE, Cline AD. Nutrient intakes and characteristics of normal weight, female military personnel consuming foods reduced in fat or energy content. Appetite 2000;34:227.
97. Yokoi K, Egger NG, Ramanujam VMS, et al. Association between plasma zinc concentration and zinc kinetic parameters in premenopausal women. Am J Physiol Endocrinol Metab 2003;285:E1010.
98. Sanstead HH. Repletion of zinc and iron deficiencies improve cognition of premenopausal women. Final Report. Galveston, TX: University of Texas Medical Branch, December 2001. DAMD17-95-C-5112.
99. Kepczyk T, Cremins JE, Long BD, Bachinski MB, Smith LF, McNally PR. A prospective, multidisciplinary evaluation of premenopausal women with iron deficiency anemia. Am J Gastroenterol 1999; 94:109.
100. Artenstein AW, VanCott TC, Sitz KV, et al. Mucosal immune responses in four distinct compartments of women infected with human immunodeficiency virus type 1: A comparison by site and correlation with clinical information. J Infect Dis 1997;175:265.
101. Evans JS, Nims T, Cooley J, et al. Serum levels of virus burden in early-stage human immunodeficiency virus type 1 disease in women. J Infect Dis 1997;175:795.
102. Jensen-Pergakes KL, Kennedy MA, Lees ND, Barbuch R, Koegel C, Bard M. Sequencing, disruption, and characterization of the *Candida albicans* sterol methyltransferase (ERG6) gene: Drug susceptibility studies in ERG6 mutants. Antimicrob Agents Chemother 1998;42:1160.
103. Kennedy MA, Johnson TA, Lees ND, Barbuch R, Eckstein JA, Bard M. Cloning and sequencing of the *Candida albicans* C-4 sterol methyl oxidase gene (ERG25) and expression of an ERG25 conditional lethal mutation in *Saccharomyces cerevisiae*. Lipids 2000;35:257.
104. Tseng J, Komisar JL, Trout RN, et al. Humoral immunity to aerosolized staphylococcal enterotoxin B (SEB), a superantigen, in monkeys vaccinated with SEB toxoid-containing microspheres. Infect Immun 1995;63:2880.
105. Wang RY-H, Grandinetti T, Shih JW, et al. *Mycoplasma genitalium* infection and host antibody immune response in patients infected by HIV, patients attending STD clinics, and in healthy blood donors. FEMS Immunol Med Microbiol 1997;19:237.
106. Sjogren MH. Clinical impact of hepatitis C infection in military active duty women. Final Report. Washington, DC: Walter Reed Army Medical Center, July 1996. 99MM5535.
107. O'Leary TJ, Teilado M, Buckner S-B, Ali IS, Stevens A, Ollayos CW. PAPNET-assisted rescreening of cervical smears: Cost and accuracy compared with a 100% manual rescreening strategy. JAMA 1998;279:235.
108. Kroening M, Robinson S, Hegge F. Expanding WebLS to support a breast cancer decision guide. PC AI Magazine, March/April 1998, vol 12. Available at *www.pcai.com*
109. Merritt D, Sodetz F, Kroening M, Littleford A, Hegge FW. Army Medical Knowledge Engineering System (MAKES)—A three-tier knowledge harvesting environment. Proceedings of the Conference on Practical Applications of Java, London, U.K., 1999.
110. Bray RM, Camlin CS, Fairbank JA, Dunteman GH, Wheeless SC. The effects of stress on job functioning of military men and women. Armed Forces Soc 2001;27:397.
111. Federman EB, Bray RM, Kroutil LA. Relationships between substance use and recent deployments among women and men in the military. Mil Psychol 2000;12:205.
112. Gunzenhauser JD. Comparative morbidity study of active duty women serving in Korea and Fort Lewis. Final Report. Tacoma, WA: Madigan Army Medical Center, May 1997. 99MM5577.
113. Wolfe J, Proctor SP, Erickson DJ, Hu H. Risk factors for multisymptom illness in U.S. Army veterans of the Gulf War. J Occup Environ Med 2002;44:271.
114. Evans MA, Rosen LN. Pregnancy planning and the impact on work climate, psychological well-being, and work effort in the military. J Occup Health Psychol 1997;2:353.
115. Rosen LH, Martin L. Incidence and perceptions of sexual harassment among male and female U.S. Army soldiers. Mil Psychol 1998;10:239.
116. Bostock DJ. Sexual assault on active duty Air Force women. Final Report. San Antonio, TX: Facilitators of Applied Clinical Trials. December 1998. DAMD17-95-2-5004.
117. Rosen LH, Martin L. Sexual harassment, cohesion, and combat readiness in U.S. Army support units. Armed Forces Soc 1997;24:221.
118. Rosen LH, Martin L. Psychological effects of sexual harassment, appraisal of harassment, and organizational climate among U.S. Army soldiers. Mil Med 1998;163:63.

119. Sadler AG, Booth BM, Cook BL, Torner JC, Doebbeling BN. The military environment: Risk factors for women's non-fatal assaults. J Occup Environ Med 2001;43:325.
120. Rosen LH, Martin L. Predictors of tolerance of sexual harassment among male U.S. Army soldiers. Violence Against Women 1998;4:491.
121. Rosen LH, Martin L. Long-term effects of childhood maltreatment history on gender-related personality characteristics. Child Abuse Negl 1998;22:197.
122. Sadler AG, Booth BM, Nielson D, Doebbeling BN. Health-related consequences of physical and sexual violence: Women in the military. Obstet Gynecol 2000;96:473.
123. Sadler AG, Booth BM, Mengeling MA, Doebbeling BN. Life span and repeated violence against women during military service: Effects on health status and outpatient utilization. J Womens Health 2004;13:799.
124. Sadler AG, Booth BM, Cook BL, Doebbeling BN. Factors associated with women's risk of rape in the military environment. Am J Indust Med 2003;43:262.
125. Rosen LH, Martin L. Childhood antecedents of psychological adaptation to military life. Mil Med 1996; 161:665.
126. Fiedler ER. Predicting military-induced stress responses in servicewomen (Air Force). Final Report. San Antonio, TX: Wilford Hall Medical Center, Lackland Air Force Base, November 1996.95MM5511.
127. Houston CS, Coates G, eds. Hypoxia: Women at altitude. Proceedings of the Tenth International Hypoxia Symposium at Lake Louise, Canada, February 18–22, 1997. Burlington, VT: Queen City Printers, Ltd, 1997.
128. Muza SR, Rock PB, Fulco CS, et al. Women at altitude: Ventilatory acclimatization at 4,300 m. J Appl Physiol 2001;91:1791.
129. Beidleman BA, Rock PB, Muza SR, Fulco CS, Forte VA Jr, Cymerman A. Exercise VE and physical performance at altitude are not affected by menstrual cycle phase. J Appl Physiol 1999;86:1519.
130. Reeves JT, Zamudio S, Dahms TE, et al. Erythropoiesis in women during 11 days at 4,300 m is not affected by menstrual cycle phase. J Appl Physiol 2001;91:2579.
131. Mawson JT, Braun B, Rock PB, Moore LG, Mazzeo R, Butterfield GE. Women at altitude: Energy requirement at 4,300 m. J Appl Physiol 2000;88:272.
132. Zamudio S, Douglas M, Mazzeo RS, et al. Women at altitude: Forearm hemodynamics during acclimatization to 4,300 m with alpha(1)-adrenergic blockade. Am J Physiol 2001;281:H2636.
133. Braun B, Mawson JT, Muza SR, et al. Women at altitude: Carbohydrate utilization during exercise at 4,300 m. J Appl Physiol 2000;88:246.
134. Beidleman BA, Rock PB, Muza SR, et al. Substrate oxidation is altered in women during exercise upon acute altitude exposure. Med Sci Sports Exerc 2002; 34:430.
135. Fulco CS, Rock PB, Muza SR, et al. Slower fatigue and faster recovery of the adductor pollicis muscle in women matched for strength with men. Acta Physiol Scand 1999;167:233.
136. Fulco CS, Rock PB, Muza SR, et al. Gender alters impact of hypobaric hypoxia on adductor pollicis muscle performance. J Appl Physiol 2001;91:100.
137. Kolka MA, Stephenson LA. Interaction of menstrual cycle phase, clothing resistance and uncompensable heat stress on thermoregulation in women. J Therm Biol 1997;22:137.
138. Kolka MA, Stephenson LA. Effect of luteal phase elevation in core temperature on forearm blood flow during exercise. J Appl Physiol 1997;82:1079.
139. Kolka MA, Levine L, Stephenson LA. Use of an ingestible telemetry sensor to measure core temperature under chemical protective clothing. J Thermal Biol 1998;23:343
140. Gonzalez RR, McLellan TM, Tenaglia SA. Heat strain in women: Comparison of model and experimental results with NBC protective clothing systems. Technical Report. Natick, MA: U.S. Army Research Institute of Environmental Medicine. North York, Ontario: Defence and Civil Institute of Environmental Medicine, 1997. TTCP-HUM-TP-6/SGU/97/KCA6.
141. Gonzalez RR, Blanchard LA, Allison WF, Gonzalez JA. Thermoregulatory sweating during cold transients and exercise: Effect of menstrual cycle phase. J Hum Environ Sys 2002;6:9.
142. Gonzalez RR, Endrusick TL, Levell CA. Biophysical properties and skin wettedness of garments with variable moisture vapor transmission rates (MVTR). J Therm Biol 1998;23:41.
143. Wallace RF, Kreibel D, Punnett L, et al. The effects of continuous hot weather training on risk of exertional heat illness. Med Sci Sports Exerc 2005;37:84.
144. DuBose DA, Wenger CB, Flinn SD, Judy TA, Dubovtsev AI, Morehouse DH. Distribution and mitogen response of peripheral blood lymphocytes after exertional heat injury. J Appl Physiol 2003;95: 2381.
145. Chang TR, Lambert GP, Moseley PL, Chapler FK, Gisolfi CV. Effect of estrogen supplementation on exercise thermoregulation in premenopausal women. J Appl Physiol 1998;85:2082.
146. Gonzalez RR, Blanchard LA. Thermoregulatory responses to cold transients: Effects of menstrual cycle in resting women. J Appl Physiol 1998;85:543.
147. Glickman-Weiss EL, Cheatham C, Caine N, Blegen M, Marcinkiewicz J, Mittleman KD. The influence of gender and menstrual phase on thermosensitivity during cold water immersion. Aviat Space Environ Med 2000;71:715.
148. Glickman-Weiss EL, Cheatham CC, Caine N, Blegen M, Marcinkiewicz J. Influence of gender and menstrual cycle on a cold air tolerance test and its relationship to thermosensitivity. Undersea Hyperb Med 2000;27:75.
149. Davis GD, Goodman MA. Stress urinary incontinence in nulliparous female soldiers in airborne infantry training. J Pelvic Surg1996;2:68.
150. Davis G, Sherman R, Wong MF, McClure G, Perez

R, Hibbert M. Urinary incontinence among female soldiers. Mil Med 1999;164:182.
151. Claybaugh JR, Sato AK, Crosswhite LK, Hassell LH. Effects of time of day, gender, and menstrual cycle phase on the human response to a water load. Am J Physiol 2000;279:R966.
152. Sherman RA, Davis GD, Wong MF. Behavioral treatment of exercise-induced urinary incontinence among female soldiers. Mil Med 1997;162:690.
153. Wright KP Jr, Badia P. Effects of menstrual cycle phase and oral contraceptives on alertness, cognitive performance, and circadian rhythms during sleep deprivation. Behav Brain Res 1999;103:185.
154. Wright KP Jr, Myers BL, Plenzler SC, Drake CL, Badia P. Acute effects of bright light and caffeine on nighttime melatonin and temperature levels in women taking and not taking oral contraceptives. Brain Res 2000;873:310.
155. Kirby AW, Comperatore CA, Arroyo S, et al. Bedtime administration of melatonin to healthy females does not alter menstrual characteristics. Technical Report No. Fort Rucker, AL: U.S. Army Aeromedical Research Laboratory, 1996. 97-04.
156. Kirby AW, Clayton M, Rivera P, Comperatore CA. Melatonin and the reduction or alleviation of stress. J Pineal Res 1999;27:78.
157. Johnson RF, Merullo DJ. Caffeine, gender and sentry duty: Effects of a mild stimulant on vigilance and marksmanship. In: Friedl K, Lieberman H, Ryan DH, Bray GA, eds. Countermeasures for battlefield stressors. Baton Rouge, LA: Louisiana State University Press, 2000.
158. Caldwell JA, Caldwell JL, Crowley JS. Sustaining female helicopter pilot performance with Dexedrine during sustained operations. Int J Aviat Psychol 1997;7:15.
159. Webb JT, Kannan N, Pilmanis AA. Gender not a factor for altitude decompression sickness risk. Aviat Space Environ Med 2003;74:2.
160. Dooley JW, Hearon CM, Shaffstall RM, Fischer MD. Accommodation of females in the high-G environment: The USAF Female Acceleration Tolerance Enhancement (FATE) Project. Aviat Space Environ Med 2001;72:739.
161. Chelette TL, Albery WB, Esken RL, Tripp LD. Female exposure to high G: Performance of simulated flight after 24 hours of sleep deprivation. Aviat Space Environ Med 1998;69:862.

Address reprint requests to:
COL K.E. Friedl
Commander
U.S. Army Research Institute of Environmental Medicine
Natick, MA 01760-5007

E-mail: karl.friedl@us.army.mil