Biological Measures and Diagnostic Tools for Gulf War Illness: A Systematic Review

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted health care topics of importance to clinicians, managers, and policymakers as they work to improve the health and health care of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of three ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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This report is based on research conducted by the Evidence Synthesis Program (ESP) Center located at the located at the Portland VA Health Care System, Portland, OR, funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

ACKNOWLEDGMENTS

This topic was developed in response to a nomination by Karen Block, PhD, Director of Gulf War Research in the Veterans Affairs (VA) Office of Research and Development (ORD) Gulf War Research Program, for the purpose of informing the planning for a state-of-the-art meeting on Gulf War Research and providing guidance for ORD funding priorities in Gulf War research. The scope was further developed with input from the topic nominators (*ie*, Operational Partners), the ESP Coordinating Center, the review team, and the Technical Expert Panel (TEP).

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The authors gratefully acknowledge the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend TEP participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

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Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

ABSTRACT

Background: Gulf War Illness (GWI) is a chronic multisymptom illness comprised of a wide range of systemic symptoms and functional impairments. We conducted a systematic review to catalogue studies (both published and unpublished/ongoing) of validated biological tests for diagnosing GWI and studies of associations between biological measures and GWI for their promise as biomarkers.

Materials and Methods: We searched multiple electronic databases, clinical trial registries, and reference lists through February 2020 for all observational studies of diagnostic tests of GWI and completed or ongoing studies of associations between biological measures and GWI. We abstracted data on study design, demographics, and outcomes. Two reviewers independently assessed the risk of bias of included studies using established methods.

Results: We did not identify any studies validating tests of biomarkers that distinguish cases of GWI from non-cases. We included 32 completed and 24 ongoing or unpublished studies of associations between GWI and biological measures that included comparator groups that provided the most useful information. Studies (n=77) with other comparator groups, no comparator group, or with N<25 were included in a table. Considering all studies, most fell within the central nervous and immune systems and indicated a significant association of the biological measure with GWI case status. Biological measures were heterogeneous across studies.

Conclusion: Our review indicates that there are no existing validated biological tests to determine GWI case status. Many studies have assessed the potential association between a variety of biological measures and GWI, the majority of which pertain to the immune and central nervous systems. More importantly, while most studies indicated a significant association between biological measures and GWI case status, the biological measures across studies were extremely heterogeneous. Due to the great heterogeneity, the focus of the review is to map out what has been examined, rather than synthesize information.

EXECUTIVE SUMMARY

AIM

We conducted a systematic review to catalogue studies (both published and unpublished/ongoing) of validated biological tests for diagnosing GWI and studies of associations between biological measures and GWI for their promise as biomarkers.

METHODS

We searched electronic databases (Ovid MEDLINE, and Ovid PsycINFO, and Ovid EBM Reviews [Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials]) through February 20, 2020 for all observational studies of diagnostic tests of GWI and completed or ongoing studies of associations between biological measures and GWI. To identify in-progress or unpublished studies, we searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). We reviewed the bibliographies of relevant articles, contacted experts, and reviewed lists of funded trials from the Department of Defense (DoD) and Veterans Affairs (VA) to identify additional studies.

We included studies of biological measures that have been examined for their promise as diagnostic biomarkers for and/or their association with GWI. We included completed and ongoing/unpublished studies of Veterans with GWI, identified using any GWI diagnostic criteria, in which the comparator population members were Veterans deployed to the Persian Gulf theater during the First Gulf War who did not develop GWI, with or without comorbid conditions (*eg*, posttraumatic stress disorder, anxiety). We excluded studies of Veterans with GWI compared to other populations (*eg*, non-deployed Gulf War Veterans, civilians), and those with insufficient sample sizes (N<25) but did summarize these studies in the Appendix to the full report.

For all included studies, we abstracted data on study design, sample size, population characteristics, case definition, comparator(s), participant inclusion and exclusion criteria, details of the biological measure of interest, and findings for measures of association as available. Data abstraction was confirmed by a second reviewer. Two reviewers independently assessed the risk of bias of included studies using established methods. Discordant ratings were resolved by consensus or an additional reviewer.

RESULTS

We identified no studies of diagnostic tests for GWI. We identified 56 studies of associations between GWI and biological measures (32 completed and 24 ongoing or unpublished).

Key Question 1: Which diagnostic tests (or test combinations) are candidates for distinguishing individuals diagnosed with GWI from individuals without GWI?

We did not identify any studies validating tests of biomarkers that distinguish cases of GWI from non-cases, regardless of the diagnostic criteria used in the study.

Key Question 2: Which biological measures have been examined for their potential association with GWI, and which among them have been shown to be associated with GWI?

We identified 32 studies of biological measures that have been examined for their association with GWI and grouped them broadly into categories under distinct biological systems: 10 studies of immune system biological measures; 10 central nervous system (CNS) studies; 5 studies of autonomic nervous system (ANS) biological measures; 1 of genetic biological measures; and 6 studies of biological measures in other biological systems (See Figure i). We also briefly summarized an additional 77 studies that examined biological measures, but do not include an ideal control group (n=72 studies) or had a sample size less than 25 (n=5 studies; See Appendix D of full report), indicated in the grey areas in Figure i.

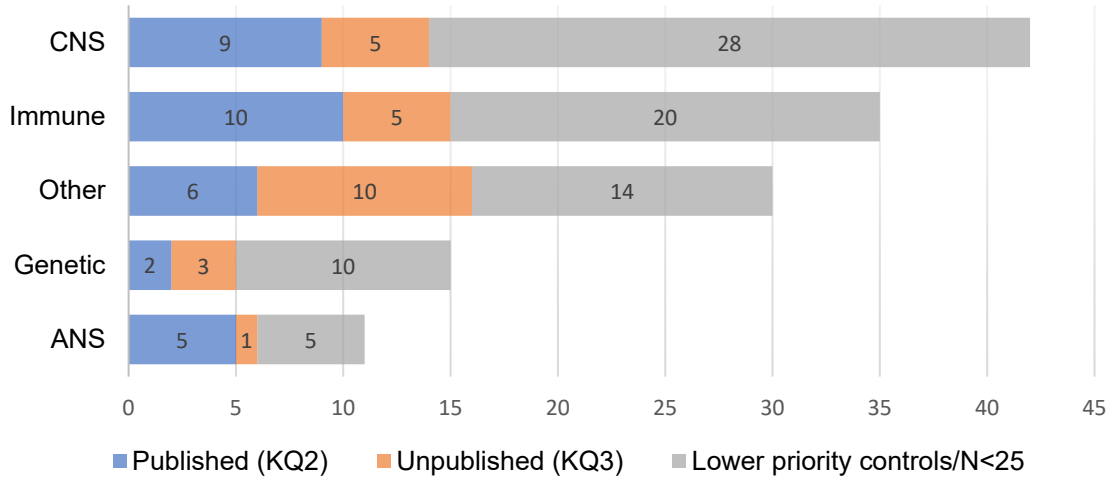
Only 1 included study used a comparator population of deployed GWVs with health conditions other than GWI; in all other studies health conditions were not reported and participants were presumed healthy.

All studies had additional methodological shortcomings. Biological measures were heterogeneous across studies, even those categorized within the same biological system, with the exception of 2 studies that had 1 replication study each.

Key Question 3: Which ongoing or unpublished research studies examine diagnostic tests or biological measures for potential association with GWI?

We did not identify any ongoing/unpublished studies examining diagnostic tests for GWI. We found 24 ongoing or unpublished studies examining biological measures for their potential association with GWI. Similar to the completed studies many are investigating measures of the immune and central nervous system (see Figure i).

Figure i. Number of studies of GWI biological measures by biological system



Abbreviations: ANS=Autonomic Nervous System; CNS=Central Nervous System; KQ=Key Question

CONCLUSION

In the current review, we sought to evaluate studies validating existing diagnostic tests for GWI, and to determine whether biological measurements with promise for further establishment as biomarkers either in completed or ongoing/upcoming studies have been demonstrated. The establishment of biological measures for GWI would allow for increased accuracy in diagnosis and potential mechanisms for treatment.

Our review indicates that there are no existing validated biological tests to determine GWI case status. It is not surprising that no such studies were found, because the case definition for GWI is still debated. In the absence of a gold standard definition or diagnostic test, the determination of biological measures to distinguish a case from a non-case is challenging.

We did identify many studies that have assessed, or are currently assessing, the potential association between a variety of biological measures and GWI. Most of the studies could be characterized as "biomarker discovery" studies and were largely designed to shed light on the potential causes of GWI. Our review indicates that biological measures within the immune and central nervous systems have more often been investigated for their potential relationship with GWI, consistent with some dominant theories of disease etiology and dysfunction, but the literature also suggests other avenues of inquiry in upcoming studies, such as the gut microbiome. More importantly, our review revealed that existing studies are insufficient for determining promising biomarkers due to the extent of heterogeneity in biological measures across studies, inadequate comparator groups, and several other methodological limitations. Future studies that employ ideal control groups, reproduce findings of existing studies, and otherwise apply rigorous methodological practices and reporting specifically appropriate for investigating potential biomarkers would contribute to the establishment of a base of targeted, highly reliable studies from which lines of investigation could grow.