Health and well-being management in the military: a systematic review of genetic studies

Nathan Parnell, K Rye, N Greenberg

ABSTRACT

Background Genetic research may have therapeutic value for mental and physical disorders and could have an indicative or preventative capacity. Little is known about the extent, form and utility of military-specific genetic research.

Method A systematic review was conducted to evaluate existing genetic well-being studies of service personnel. The review specifically aimed to ascertain the current state of knowledge and feasibility of using genetics to aid recruitment and health management within military populations. Databases searched included MEDLINE, Embase, PsycINFO and Web of Science for relevant studies. Papers were rated using a genetics-specific quality assessment framework.

Results Ten papers were included within the final review, with seven mental-health-focused and three physical-health-focused genetic studies found within military populations. Eight papers considered candidate genes, one gene expression and one study was an outline of a future study of significant interest. Genetic commonalities were derived to yield shared physiological pathways. The 10 reviewed papers revealed moderate quality based on quality assessment.

Conclusions Current genetic research within military populations is limited. Further studies on genetics, cost effectiveness, ethics and continual monitoring need to be explored before considering any movement toward clinical translation.

INTRODUCTION

The influence of genetics on mental or physical health has been a subject of great interest and research for many years. Although the ethical view on using genetics to inform health management is mixed, specific genes have now started to be empirically validated for both physical Alzheimer’s and some cancers and to a lesser degree non-dementia mental health conditions, including most notably psychosis and suicide.

While the research carried out on this topic is predominantly conducted on civilians, the potential benefits of indicative, diagnostic or treatment informed genetic information are of interest for specific populations. Derived information might provide findings relevant to health and subsequent organisational costs. Given past and recent conflicts, alongside the unique roles or environments they may be exposed to in training, combat or daily life, one specific population of interest is the military. Although not directly stating a use for the military, genetics has also been speculated by the Ministry of Defence as a future trend of general public health research and management.

Research has shown these roles or environments to cause problems on an individual and organisational level. Post-traumatic stress disorder (PTSD), depression, anxiety and alcohol misuse have been found to be common in some groups of UK military personnel being linked to stressors such as combat or overstretch of staff. Physical problems such as stress fractures and other musculoskeletal problems are also significant health issues for military populations being linked to high physical demands and training requirements of the job. As such, organisationally, the implications of serving individuals experiencing a mental or physical health problem are significant. Last year alone, mental health staff working at the UK military’s Departments for Community Mental Health saw 6210 service personnel for mental health assessments or treatment. Furthermore, 1930 personnel have been medically discharged for mental health reasons since 2007. Additionally, up to 48% of UK military recruits sustain physical injuries during training, leading to withholding of training completion and thus productivity and personnel throughput into active service. Within the UK and elsewhere, although there are numerous safeguards in place to pre-empt or manage health risks, the ability to predict who will develop mental or indeed physical health problems remains limited.

Although limited at present, services using predictive genetic tests as pre-emptive indicators of future risk are being offered in both NHS and via self-referral in the private sector to inform at least clinical monitoring for present or potential health problems. This movement toward gene informed health management has also been explored in a US military context surrounding PTSD. Preliminary applications and future usage currently were discussed in terms of identifying predictive or indicative PTSD biomarkers such as from a combat injury.
Most relevant research has been conducted within the civilian sphere, whereas military populations are exposed to a range of stressors that are not commonly found within other areas of civilian life. Replication of research within military populations may therefore be important to understand its potential—be it predictive or identifying those who may already have a health problem—when considering this niche pool of individuals with specific occupational and health management needs. Early work\(^2\) has already considered the use of genetic-based research, yet strong foundations for such work need to continuously be established for any clinical translation in the future.

In order to investigate whether the use of military-specific genetic research may impact on prediction or identification of existing health problems within military populations, this review focuses on evaluating the current research into the use of genetic factors on the health and well-being of a military population. The applications of such research within a military setting will be considered, along with the implications and considerations needed alongside genetics, such as ethics and acceptability, in order to evaluate applicability to such populations in the future.

### METHODOLOGY

#### Selection of studies

Searches were limited to primary research papers published in peer-reviewed journals in the English language. Inclusion criteria were those papers that reported on or tested specific genetic associations, markers or uses of these specific markers that were of relevance to any aspect of physical or mental well-being of military personnel. Any papers outside of this remit were excluded.

#### Conducting the review

Relevant search terms were composed of those both directly and indirectly related to genetics in general, with the preface of each search term then adding the military component of the research (see online supplementary material 1 for search terms and strategies).

Authors conducted these search terms within Web of Science and the Ovid Database (Embase, PsycINFO and Medline); the senior researcher provided oversight of the search process. Resulting citations were downloaded to EndNote software version X7, where duplicates were removed. Titles of papers that were included were any that relayed any form of genetic and military population. Abstracts of papers that were included were those that summarised any genetic associations, markers or uses of these specific markers within the studies or outlines. All papers were evaluated by the same reviewers for initial inclusion via three layers of screening; all irrelevant references were excluded.

#### Data extraction and quality assessment

A standardised approach was used to extract relevant information pertaining to the aim of the review from the remaining papers. The following were included: lead author, year of publication, country, aims of the paper, study design, participants and demographics, method of genetic platform/extraction and analysis, number of single-nucleotide polymorphisms tested (if applicable), candidate genes identified, any other psychometric or psychological measure, mental or physical health focus, results, conclusions and limitations.

Due to the specific nature of genetic research, a standardised Quality Assessment Framework (QAF) Checklist constructed for this field was used.\(^2\) This has been previously applied to systematic reviews of genetic research within physical health.\(^2\) Each quality assessment score was calculated out of 13 items (1=assessment item present in paper; 0=not present) and their mean percentage derived from the scoring system.

### RESULTS

#### Screening

A total of 6410 citations were identified, of which 10 papers remained after three layers of screening (see figure 1).

#### Quality assessment

The purpose of this review was to evaluate the current state of genetic research pertaining to health and well-being within military populations. Although methodological rigour is important, the paucity of genetic research within such a unique population needs to be taken into consideration when reviewing the quality from a standardised perspective, alongside certain factors such as age of research and genetic methods available at the time.\(^2\)

The majority of the studies were of moderate quality. See figure 2 for overview of criteria items and percentage results for papers.

![Review process screening](image)

**Figure 1** Review process screening. Filtering derived 10 papers for review post title, abstract and full text screening.
A total of 10 papers were identified from search terms and included within the final review.\textsuperscript{21–24,26–32} The review yielded seven mental-health-focused and three physical-health-focused genetic studies in military populations. Of the three physical health papers, six were focused on stress fractures, one on sickle cell and one on health coaching for risk of conditions. Of those seven mental health papers, six were focused on PTSD, while one focused on stress-induced psychosis. Regarding the genetic focus of papers, eight candidate gene, one gene expression study—an ‘epigenetic’ approach that looks at how modification to genes’ influence on the body changes organisms or processes, rather than how the gene or genetic code itself plays a role—and one future study outline of significant interest were identified. Countries of origin included six from the USA,\textsuperscript{21,25,26,28,30,32} two from Israel,\textsuperscript{29,31} one from the Netherlands\textsuperscript{24} and one from Greece.\textsuperscript{27} Thus far, from the literature search, research within the UK in relation to genetic research within a military population was not found.

Methodologically, only three studies declared any form of power adjustment or consideration\textsuperscript{25,27,28} to account for correct sample size, along with five studies adjusting for multiple testing of statistical analysis of data.\textsuperscript{24,25,27,29,30} Sample sizes ranged from 16\textsuperscript{26} to 2243.\textsuperscript{27} Regarding health focus of papers, of the included papers, five focused on combat-related PTSD, two on treatment response to PTSD or coronary heart disease/type 2 diabetes, one on stress-induced psychosis symptoms, one on stress fractures and one further paper on awareness of genetic traits. Eight of the papers aimed to provide results on predictors or susceptibility markers for health problems, and the remaining two focused on health management and coaching using genetic information. The predominant method of DNA extraction was blood based\textsuperscript{21,24–26,28,30–32} with two using saliva samples.\textsuperscript{27,29} The two saliva extraction studies were also two of the highest sampled investigations.

Regarding total markers, 14 different genetic markers were identified and researched (see Table 1). One gene expression study\textsuperscript{26} identified 67 dysregulated gene markers. Of the 14 specific markers identified, 2 overlapped in separate papers, with the remainder being singular studies or within review papers outside of a military population. Regarding ethnicity, five of papers included participants of European or non-Hispanic ethnicity, with two using black or Hispanic origin samples. The remaining three did not reveal any ethnic demographics on their sample. Only one paper considered ancestry\textsuperscript{24} along with one considering family traits.\textsuperscript{21}

Only one physical health paper explicitly outlined any ethical considerations in using genetics in military health management,\textsuperscript{28} outlining the potential for genetics to be interpreted as deterministic of disease or provide false assurance to those who do not have any risk marker. No ethical considerations were noted within the mental health papers.

**DISCUSSION**

This review focused on the field of genetic factors surrounding the mental and physical health of military populations. The search terms derived a total of 6410 citations, of which only 10 papers met the inclusion criteria for this review. The predominant focus of the reviewed papers was combat-related PTSD. The search identified that the recent focus within genetically applicable research to military populations has been on mental health and the possibilities of screening for genetic markers.\textsuperscript{19,20} However, the results suggest that success in predictive or susceptibility markers is at best mixed.

Considering DNA extraction methods and efficiency, eight papers used blood-based methods and the remaining two used saliva extraction, of which yielded some of the highest sample sizes.\textsuperscript{27,29} This could be explained by military personnel having varying roles that encompass a high level of mobility, leaving DNA extraction to become difficult due to absence during deployment, high workload or travel. The predominant method of blood-based extraction is also time consuming in itself and...
Table 1  Genetic and pathway commonalities: reviewed papers and papers of interest

<table>
<thead>
<tr>
<th>Gene code</th>
<th>Activity and action</th>
<th>Mental or physical health (author)</th>
<th>Sample size (author)</th>
<th>Method of DNA extraction (author)</th>
<th>Citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC6A4 (5-HTTLPR)</td>
<td>Serotonergic transportation</td>
<td>Mental: PTSD and depression (Wald et al²⁹ and Wang et al²⁹); working memory, executive functioning, decision making and social/emotional functioning (Weaver et al³⁰)</td>
<td>722 (Wald et al²⁹)</td>
<td>Saliva swab (Wald et al²⁹); blood (Wang et al²⁹)</td>
<td>3</td>
</tr>
<tr>
<td>COMT polymorphism (Val158Met)</td>
<td>Affects enzyme activity and associated with stress-induced psychogenic symptoms</td>
<td>Physical: traumatic brain injury recovery in working memory, executive function, decision making (Weaver et al³⁴)</td>
<td>2243 (386 in follow-up) (Stefanis et al²⁷)</td>
<td>Saliva (Stefanis et al²⁷)</td>
<td>2</td>
</tr>
<tr>
<td>Coronary heart disease: SNP rs10757274 9p21 locus of chromosome 9. Type 2 diabetes: SNPs rs7903146, rs1801282, rs5219</td>
<td>Risk markers identified as most likely aetiology for CHD or T2D</td>
<td>Physical: CHD and T2D genetic information added to health coaching and risk coaching to see if it benefits (Borderstrasse et al²³)</td>
<td>Only study outline is published</td>
<td>Potential Blood</td>
<td>1</td>
</tr>
<tr>
<td>Androgen receptor gene CAG repeat</td>
<td>Potential relation to bone density</td>
<td>Physical: stress fractures link (Yanovich et al³¹)</td>
<td>454</td>
<td>Blood</td>
<td>1</td>
</tr>
<tr>
<td>FKBP5, GILZ and SGK1 (van Zuiden et al³⁵)</td>
<td>Implicating GC and GC receptors and links to PTSD, fatigue and depression (van Zuiden et al—non-genetic) and to just PTSD (Yehuda et al³²)</td>
<td>Mental: PTSD, fatigue and depression (van Zuiden et al³⁵) and just PTSD and treatment response (Yehuda et al³²)</td>
<td>16 (Yehuda et al³²)</td>
<td>Blood (Yehuda et al³²)</td>
<td>FKB5: 2 papers</td>
</tr>
<tr>
<td>Hgb-S</td>
<td>Sickle cell cause</td>
<td>Physical: sickle cell (Binder et al³³)</td>
<td>1000</td>
<td>Blood</td>
<td>1</td>
</tr>
<tr>
<td>SKA2</td>
<td>Involved in GC receptor transactivation and links to cortisol reactivity and risk of developing PTSD</td>
<td>Mental: PTSD development (Boks et al³⁴)</td>
<td>94</td>
<td>Blood</td>
<td>1</td>
</tr>
<tr>
<td>D2A1 allele of the DRD2 locus</td>
<td>DRD2 has been implicated in alcoholism, and explored whether D2A1 allele of this is also related</td>
<td>Mental: PTSD role alongside substance abuse (Comings et al³⁶)</td>
<td>56</td>
<td>Blood</td>
<td>1</td>
</tr>
<tr>
<td>67 genetic markers</td>
<td>Immunity regulation</td>
<td>Mental: PTSD and immunity regulation (Glatt et al³⁰)</td>
<td>50</td>
<td>Blood</td>
<td>1</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; GC, glucocorticoid; PTSD, post-traumatic stress disorder; SNP, single-nucleotide polymorphism; T2D, type 2 diabetes.
presents difficulty with either reluctance due to needle use or obvious problems in self-gathering blood samples. Although little research has been conducted in comparing DNA extraction methods for genetic studies, research has shown that saliva is becoming an accepted and reliable method of DNA extraction, with applications in self-gathered and field-gathered DNA.18 33

Throughout the papers, commonalities have also become apparent between genes and shared biological pathways. Table 1 demonstrates commonalities between genetic pathways and mechanisms highlighted within the main review papers, with supporting information from other papers of interest found within the review search. Genes involving the serotonergic (5-HT variant), dopaminergic (Catechol-o-methyl transferase (COMT)) and glucocorticoid pathways were highlighted in three,19 30 14 two,36 37 and three24 32 35 papers, respectively, from both included and interest papers34 35 in relation to PTSD in the military. These pathways are also implicated in the development of depression,36 psychosis37 and regulating immunity functioning.38 There are also supporting studies showing co-morbidity between these disorders and PTSD in military populations, predominantly depression.39 40 Symptoms that can be present in psychosis or dissociation have also been shown to be co-morbid and related to PTSD41 along with immune disorders being prevalent in military populations.42 Although these results may be indicative toward areas of interest within neurotransmitter pathways, interpretation of these results in relation to predictive or future tests is tentative given that these pathways can be implicated in several disorders. This further adds to the complex picture of disentangling the biological picture, and more exploration would be beneficial in exploring pathways that might be implicated in co-morbidities or isolating a pathway to health problems, for example, PTSD specifically.

Of note is that only one paper stated any ethical considerations of using genetic information for health management of military personnel, relating to determinism or fatalism of this information.28 Interestingly, this study focused on physical health, with no mention of ethical considerations within mental health research. Only one small-scale qualitative study within a paper of interest considered the ethical perception of the use of psychiatric genetics within a military population experiencing mental health problems. Within this, despite negative themes emerging from the option of testing—discrimination in various life domains (67% of sample) and disappointing results/uncertainty of causality (22%)—the predominant perception of veterans was one of a positive nature, with two main themes of advances for medicine (89% of participants) and understanding and helping others (67%) emerging. However, despite this small-scale study (n=9), there is still a current rise in considerations on the use of genetic information and the complexities of managing moral and legal duties on receiving such personal results for employment or health management.41 44 As such, careful consideration needs to be taken when devising future research, particularly if it might pose significant ethical risks associated with an individual’s career in the military. Further, research success logically hinges on acceptability, within the military and the wider community, in order to effectively recruit participants. Therefore, this area is vital to explore further as a foundation on which to build justification and feasibility within further studies.

Following on, the method of genetic information collection and use of the results may also affect how acceptable the use of genetic information might be perceived and subsequently how successful further research may be. One indicator of where this is at present in the public eye is the availability of easily accessed genetic testing. The widespread availability of such services is increasing with companies offering self-testing services for indicative or ancestral purposes.18 One factor that potentially makes this acceptable is offering the freedom of choice whether to self-test or not. This may mitigate the social impact of genetic testing and work towards the use of genetic information being viewed as more mainstream than new science. Importantly, companies such as 23andMe also indicate that although linked to marker genes, these tests are only indicative and not deterministic of risk or causality in disorders or ancestry. In the case of occupational genetics, if this method is not seen as acceptable information and yet implemented—as a voluntary or routine measure in screening or existing health checks—this could lead to further stigma already noted.4 Identification of how individuals and society views this method is key for building any form of ethical implementation model when and if the use of genetic information becomes feasible to do so.

When or if this is achieved, alongside, more research is needed to differentiate internal genetic processes that influence PTSD development aside from other external and contextual-based associations, such as attention bias in relation to how people perceive threats or confounding or co-morbid problems such as addictions.25 Primary steps have been taken to address this in broadening guidelines for identifying biomarkers encompassing risk, resilience, diagnoses and treatment response rather than just predictive markers.19 Consideration of DNA and individual genes as well as gene expression, neurotransmitters or immune function and markers has been noted within these and emerging research,43 46 which may reflect their suggestion that disorders such as PTSD may encompass more than one gene given the various subtypes and presentations, yet more work is needed.

Overall, methodological quality of the papers was moderate as rated by QAF. However, there was a predominance of candidate gene approach, omitting study designs such as genome-wide association studies or environment interaction studies. This potentially created a limitation on how high certain studies could score due to some criteria assessing factors relating to other genetic research methodology, as well as this tying in with other research being conducted at a time that may not reflect genetic methodology comparable to that in recent papers.21 This may also be indicative of a need for the use of different genetic methods in the future within military populations, with larger sample sizes and subsequent power considerations given the large variation in existing studies in this review, efficient DNA extraction methods to draw in larger samples and rigorous analyses plans with corrections for multiple testing. Varying genetic approaches to methodology such as epigenetics have shown to have potential as alternatives due to considerations of the effect of environmental factors on genes, further genetic processes and its subsequent implications for clinical or public health.47 Given the extraordinary environmental and physical situations that military personnel can encounter, utilisation of varying methods could prove useful given the similarity of need within future military research.

Further broadening of sample demographics also needs to be considered; individuals from western countries, or countries on or near the Mediterranean were the predominant sample for relevant research, being drawn from areas such as the USA, the Netherlands, Greece and Israel. Given the diversity of these and the UK Armed Forces,48 further studies may benefit from accounting for wider ethnicities and demographics in order for this form of research to include all personnel.

Given the state of military involvement in conflicts at present, research would also benefit from continuing to explore varying areas seen previously27 28 as genetic research can also encompass

treatment or stress response, something which can be broadened to benefit all military recruits and trained personnel throughout their service time rather than a focus on those who would be on the front-line and at risk of combat trauma. For physical conditions such as stress fractures, the paucity of genetic research looking into such an important problem is indicative of further research into this area. Given the statistics pertaining to injury during training alone, this could be one area of focus to maximise individual and organisational health if taken further.

As such, the current state of genetic research to improve the health of military populations presents a complex picture. Recent research suggests that methodologies can be regarded as comprehensive yet encapsulates the complexity by acknowledging similar pitfalls to research noted above, namely; finding further overlap of genetic markers in PTSD and immunological disorders, confounding any shared physiological pathways; lack of replication in a second sample; and specificity in relating their significant finding to a specific population. Further, even if, or when, specific genetic markers that have utility are identified, more investigation is needed—in military populations—in relation to the feasibility of successful DNA markers and extraction techniques for use in a population that has high mobility and throughput. More work is also needed to better understand the ethical aspects of the use of genetic screening in the Armed Forces in order to be able to understand the implications of using this method.

Possible future directions
At present, the results suggest that currently there is insufficient evidence to support consideration of military use of specific genetic markers to improve the health and well-being of personnel. However, there is considerable scope for future research into this topic within such a population as the field develops. While it is not possible to be certain whether genetic screening or management for personnel in specific roles or branches of militaries will be seen as helpful in the future, it is notable that most identified research focused on possible utility for personnel deployed on operational duties. In particular, studies of preventative approaches to PTSD were especially evident in our searches. Stress fractures also seem to be an important military health topic, which has been the subject of genetic marker research, yet this is fractional in size relative to the extent of this physical problem within the military at present. There was some evidence of a possible role for genetic screening with treatment outcomes and traumatic brain injury response markers. However, once again research seems to be too preliminary to start wider translation—research or clinically—with limited scope on a few markers and small sample and power; therefore, tentative steps needs to be taken in this direction. Further, if target genes or epigenetic biomarkers are identified as being clearly related to risk of poor health, then consideration may also be given for health advice to improve the outcome of those found to be at risk of certain problems given more evidenced-based research into concrete associations.

Despite the above, it is apparent that all future research on suitable genetic, epigenetic or biomarkers being identified will need to consider the ethical implications and perception of genetics—both individual and societal—when considering the use of this approach within the Armed Forces. One avenue to explore is investigation into the acceptability of such methods; such information will be key to inform whether future research into the use of markers may be well received in the military, and the results of such studies would be relevant to roll out a programme at the point that it becomes feasible to do so. The results of such research would also be of use to help justify the future use of genetic, epigenetic or biomarkers in the eyes of personnel.

Limitations of our review
There are several limitations to this review. Database searches may miss out papers that only state specific gene names that, for obvious reasons, are not included in our search terms given the large variations and number. This review was solely focused on the potential for the use of genetic research to improve the health and well-being of military populations. As this does limit the scope and omit genetic research that may be more widely applicable for use within the general population, a serious consideration is that the military is a unique participant pool that can experience extraordinary physical, social, emotional and environmental factors that are not readily replicable within civilian life.

CONCLUSIONS
Genetic research within military populations is limited. Given the complexity of the current state of the field in this population, further studies on genetics and biomarkers, along with the ethical and logistical implications of such research need to be explored to ensure that a robust empirical launch pad is in place before considering any implementation of this approach in research studies or as clinical translation.

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