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Psychophysiological Measures of Stress in Caregivers of Individuals with Autism Spectrum
Disorder: A Systematic Review

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Abstract

Objective: Parents of children with Autism Spectrum Disorder (ASD) often self-report heightened levels of stress and physical health problems. This paper reviewed studies assessing physiological measures of stress among parents of children with ASD.

Methods: Systematic database searches identified 15 studies meeting inclusion criteria. Studies were reviewed to determine: (a) control group characteristics; (b) caregiver and care recipient characteristics; (c) setting; (d) physiological measures employed; (e) physiological outcomes; and (f) stressor type. A measure of methodological quality was also applied.

Results: Salivary cortisol was the most common physiological measure employed. A pattern of blunted physiological activity emerged within the reviewed studies, though some studies reported normal or even higher physiological activity among this population.

Conclusions: Findings suggested dysfunction of the hypothalamic-pituitary-adrenal-axis and autonomic nervous system for some, but not all, parents of children with ASD. Further research is warranted.

Keywords: Autism; parenting stress; health; physiological activity; cortisol; cardiovascular

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Parenting can be a stressful experience for all parents at times [1], but this stress is likely to be more pronounced among parents of children with disabilities [2]. Of all the childhood developmental disorders, Autism Spectrum Disorder (ASD) has been found to give rise to one of the most complex networks of stressors [3]. Parents of children with ASD have frequently been reported to experience significantly higher levels of stress than parents of children with typical development or other disabilities [4 – 7]. Hayes and Watson [8] conducted a meta-analysis of studies comparing parenting stress in parents of children with and without ASD, and reported a large effect size indicating that parents of children with ASD self-report significantly higher levels of stress than parents of children with typical development and other disabilities.

Chronic stress, such as that often experienced by parents of children with ASD, is known to have adverse effects on a range of physical and psychological outcomes [9]. Consistent with this observation, parents of children with ASD have been found to report heightened levels of health problems. Parents of children with ASD have reported poorer health symptoms and/or more illnesses in comparison to parents of children with typical development [10 – 13] and parents of children with other disabilities [14]. However, while parental self-report is useful for determining perceived wellbeing, relying exclusively on parental self-reports of stress and health can be problematic for a number of reasons. Parental self-reports are subject to potential bias [15]. Physiological measures do not always correlate well with self-reported stress [e.g. 12] and those who report the highest levels of stress do not necessarily demonstrate the highest physiological responses to stressors [15]. Thus, parental self-report provides limited information about the physiological impact of stress related to parenting a child with ASD, and its implications for health. Use of physiological measurement has been recommended for studies of stress [15], and the extant stress literature offers many approaches for measuring the physiological systems affected by stress. Such measures are based on substantive research documenting reliable physiological responses to stress, both acute and chronic.

Physiological measures of the stress response

Exposure to a physical or psychological stressor triggers the stress response [16], which leads to activation of two major systems, the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA)-axis. The ANS is separated into two branches: the *sympathetic* nervous system, responsible for mobilising the body for a fight-or-flight response, and the *parasympathetic* nervous system, which conserves energy and attempts to maintain homeostasis [16]. The HPA-axis, which is responsible for neuroendocrine adaptation, also facilitates the fight-or-flight response and attempts to maintain homeostasis within the body [17]. Homeostasis is the body's process for maintaining optimal bodily functioning in response to environmental changes, in order to avoid damage; however, attempts to maintain homeostasis long-term as a result of chronic exposure to psychological stressors can lead to wear-and-tear, with potential for adverse effects such as fatigue, hypertension (i.e. blood pressure), cardiovascular disease, and damage to immune function [16].

There are many non-invasive methods that can be employed to measure ANS and HPA-axis activity, and research has demonstrated the link between these measures and health. Chronic activation of the HPA-axis can increase reactivity to stressors and is associated with increased health risk [17]. The most common measure of HPA-axis activity is the hormone cortisol, which is produced in response to activation of the HPA-axis. While cortisol can be measured in blood samples, salivary cortisol has also been found to act as a marker for HPA-axis activity [18], providing a non-invasive alternative to venepuncture (i.e. puncturing veins). Cortisol has a strong basal diurnal profile, with a characteristic increase of approximately 50-60% in the first 30-45 minutes after awakening (known as the cortisol awakening response), a rapid drop over the first few hours after waking, and a gradual decline throughout the rest of the day [18]. Dysregulation of the morning cortisol awakening response is associated with negative outcomes such as depression [19], while blunted cortisol reactivity and low daily cortisol levels (i.e. hypocortisolism) can result in decreased immunity and increased vulnerability to stress-related diseases [20].

Measures of ANS activity within the literature tend to be more varied, and include measures of electrodermal activity, alpha-amylase, and cardiovascular measures. Skin conductance level, a measure of changes in electrodermal activity, is one of the most frequently studied physiological

markers of ANS activity [21]. Skin conductance levels can be measured non-invasively, typically by monitoring reactivity to experimental stressors through electrodes attached to the skin. Electrodermal activity measures are associated with stress-related psychophysiological disorders [22]. Alpha-amylase, an enzyme produced when the ANS is activated, is another measure of ANS activity, and like cortisol, it can be measured non-invasively using saliva samples [23]. Chronic activation of the ANS is known to be associated with health problems such as immune suppression [24].

With respect to cardiovascular measures of ANS activity, different indices of cardiovascular functioning are often measured. Laboratory-based methods for inducing cardiovascular reactivity to psychological stress are common, as they allow for a high degree of experimental control [25]. These approaches can include measurement of blood pressure, heart rate and heart rate variability when exposed to an experimental stressor [26]. Use of ambulatory blood pressure monitoring has also been reported within the literature [27], and involves repeated measurements of blood pressure and heart rate over an extended period in the natural environment. The reactivity hypothesis, which posits that higher cardiovascular reactivity is indicative of increased cardiovascular disease, is well established [28], and both cardiovascular reactivity to experimental stressors and ambulatory cardiovascular activity have been found to predict cardiovascular disease risk, particularly hypertension (i.e. high blood pressure) and even mortality [27, 29]. Thus, many non-invasive methods of measuring ANS and HPA-axis activity exist, with their links to health well established.

Aims of the present study

A strong link has been established between HPA-axis and ANS markers and increased health risk, while parents of children with ASD are known to report chronic stress and increased health problems and illnesses. Thus, incorporating these physiological measures into research investigating stress within this population would likely further our understanding of the underlying processes involved in chronic stress and their links to poorer health among parents of children with ASD. In recent years, there has been a growing focus on such physiological correlates of stress and health among parents of children with ASD. However, this body of literature is in its infancy and to date, no review of existing studies has been conducted. Thus, the aims of the review were to (1) identify the

types of physiological measures employed within the body of literature, and (2) to synthesise outcomes of physiological measurement of stress in this population. A quality rating was also applied.

Methods

Search Procedure

Articles were identified by conducting comprehensive searches on the following databases in May 2017: EBSCOHost, ERIC, PsycINFO, Medline, Scopus, and Web of Science. Searches were conducted by inputting *autis**, *ASD*, *developmental disabil**, or *Asperger*, in combination with the following keywords: *stress*, *cortisol*, *heart rate*, *blood pressure*, *cardiovascular*, *cardiac*, *vasopressin*, *growth hormone*, *antibod**, *immun**, *catecholamine*, *electrodermal*, *alpha amylase*, *C reactive protein*, *endocrine*, *hormon**, *physiolog**, *psychophysiol**, *autonomic*, *galvanic skin response*, *secretory immunoglobulin A*, *reactivity*, or *responsivity*. These search terms were entered in combination with a third set of keywords: *mother*, *father*, *parent**, *care**, or *family*. There was no restriction on the year of publication, but only papers published in the English language were considered for inclusion. Additionally, the reference list of any study that met inclusion criteria was hand searched to determine if any additional papers met the inclusion criteria.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (a) the study was published in a peer-reviewed journal; (b) included primary caregivers of persons with a reported diagnosis of ASD, and; (c) measured at least one psychophysiological correlate of stress or health (e.g. cardiovascular activity, cortisol levels, antibody responses). Studies were excluded if they: (a) included only self-report measures of stress amongst caregivers of persons with autism; or (b) included only caregivers of individuals that were not diagnosed with ASD. Studies that included caregivers of individuals with other diagnoses were only included if the data for caregivers of individuals with ASD could be extrapolated from the overall sample. Studies that reported on use of physiological measurement to evaluate intervention effects were only included if baseline data could be extracted from those studies (i.e. data were not extrapolated from phases in which effects of interventions on physiological responding were being measured).

Selection of Articles

All abstracts returned during the electronic search were reviewed by the second author to determine their eligibility for inclusion. All papers were then reviewed by the first author, and there was 100% agreement between both reviewers that all selected papers met criteria for inclusion.

Study Categorisation

Included studies were categorised according to the focus of the study. They were categorised as either: (1) *baseline physiological functioning*, defined as any study that did not include an experimenter-established stimulus condition change or manipulation by the experimenter that differed from baseline such as a stress reactivity test (e.g. baseline cardiovascular activity, cortisol levels on waking, etc.); or (2) *physiological reactivity*, defined as any study that included an experimenter-established stimulus condition that differed from baseline, which could be conducted in an experimental setting (such as a clinic, laboratory or medical centre) or in a non-experimental setting (such as the participant's home or place of work). One study [30] included an intervention phase evaluating the effects of a service dog on salivary cortisol and parent-reported stress. Use of physiological measurement to evaluate intervention effects was outside the scope of the review, since it did not fit into either baseline or reactivity categories. It was not considered appropriate to create a third category for intervention studies, since only one such paper was identified. As a result, the study was included in the *baseline physiological functioning* category, with data only extracted for the baseline phase.

Data Extraction

Across both categories, data were extracted from studies on the type of measurement, outcomes, and other relevant study characteristics.

Physiological Measures. Included papers were reviewed in order to identify relevant codes for physiological measures. Codes used across studies that measured baseline physiological functioning and physiological reactivity have been defined in Table 1. For studies that measured *baseline physiological functioning*, cortisol measures were also identified as either: (1) *salivary*, if measures were obtained from saliva samples; or (2) *serum*, if measures were obtained from blood samples.

(Insert Table 1 about here)

Physiological Outcomes. Data relating to physiological measurement were extracted from the studies. Outcomes relating to non-physiological measures (e.g. self-report measures of stress or health) were reported only if they were presented in analyses with physiological measures (e.g. if a study investigated the relationship between physiological and non-physiological measures).

Stressor. For studies coded as assessing *physiological reactivity*, data on the type of stressor used to elicit a physiological response were extracted.

Control Group. Information was extracted on the type of control group included if applicable (e.g. caregivers of typically developing children or children with other disabilities), as well as the sample size for the control group.

Caregiver and Care Recipient Characteristics. Data were extracted on the number of caregiver participants (i.e. caregivers of children with ASD) within the study, and the age and gender of the both the caregiver and care recipient, if reported.

Setting. Data were extracted on the setting in which the study was conducted. Specifically, the setting in which physiological measures were collected. There were two codes used: 1) *Laboratory*, which referred to any laboratory, clinical or medical setting; and 2) *Home*, which referred to the participant's home or natural setting.

Quality Assessment

The assessment of methodological quality of studies is recommended within systematic reviews [e.g. 31]. Given that the present review included non-interventional psychophysiological studies, with both baseline and reactivity papers, many commonly used quality assessment tools were not suitable for use. One quality rating tool for use in a review of non-interventional psychophysiological studies has previously been developed and employed within a systematic review of physiological reactivity among persons with ASD [32], and is based on Farrington's [33] quality standards. Lydon et al.'s [32] quality assessment tool did not incorporate baseline psychophysiological studies, so the tool was adapted for use in the present study.

The adapted quality rating tool used in this review is presented in Table 2. With the exception of some slight rewording, the same structure and items as used by Lydon et al. [32] were included, but

two items that did not apply for the current review were removed. These items referred to habituating participants in advance of the study, which is more applicable to children with ASD (the focus of Lydon et al.'s review) than adult caregivers (the focus of the current review). The rating tool included four key categories (descriptive validity, internal validity, external validity, and statistical conclusion validity). All categories except external validity included multiple items, with an overall total of 20 items for studies measuring physiological reactivity and 18 items for studies measuring baseline physiological functioning. External validity was either scored as 3 ('*very good*'), 2 ('*adequate*'), 1 ('*poor*'), or 0 ('*very poor*'). All other items were either marked as present or absent. These scores were then added up for each of the 4 categories, with each category awarded a score from 0-3 as follows: 3 ('*very good*') if 91% or more of the criteria in the category were met; 2 ('*adequate*') if 71-90% of the criteria in the category were met; 1 ('*poor*') if 51-70% of the criteria were met; or 0 ('*very poor*') if 50% or less of the criteria in the category were met. Scores from each category were then added, providing an overall rating of between 0-12 for each study. For each category of studies (i.e. baseline physiological functioning and physiological reactivity), a median split was then performed using total scores. Studies that received a score equal to or above the median split were classified as being of a higher quality and studies that received a rating below the median split were classified as being of a lower quality.

(Insert Table 2 about here)

Interrater Reliability

To ensure the accuracy of data extraction and quality assessment ratings, interrater reliability was calculated to assess the agreement between two independent raters across all included studies. Agreement was defined as reviewers selecting the same data extraction classifications for a study, or arriving at the same quality assessment rating. A non-agreement was defined as observers recording a different classification for a study or arriving at a different quality assessment rating. Mean inter-rater agreement was calculated by dividing the number of agreements by the number of agreements plus non-agreements, and multiplying by 100. Mean interrater agreement for data extraction was found to

be 83.9% for baseline studies (range: 50%-100%) and 81.3% (range: 75%-100%) for reactivity studies. Overall mean interrater agreement across all studies was 82.3%. For quality ratings, mean interrater reliability was 90.3% (range: 71.9%-96.9%) for baseline studies and 93.4 % (range: 76.5%-100%) for reactivity studies. Overall mean interrater agreement for quality ratings across all studies was 92.2%. In the case of non-agreements, consensus was achieved through discussion between raters.

Results

A total of 15 studies met inclusion criteria, 11 (73%) of which focused on measuring baseline physiological functioning in caregivers of individuals diagnosed with ASD, and four (27%) of which focused on physiological reactivity in this population. The studies identified were relatively recent, with papers having been published between 2010 and 2017. These studies reported on baseline physiological functioning and physiological reactivity to stress for 704 and 143 caregivers of individuals with ASD, respectively. Results have been presented separately for studies that assessed baseline physiological functioning or physiological reactivity. Within each category, findings have been presented for the types of physiological measures, outcomes, other characteristics and quality assessments, in line with the research aims.

Baseline Physiological Functioning

Data for studies that measured baseline physiological functioning are presented in Table 3.

(Insert Table 3 about here)

Physiological Measures. To aid interpretation of the types and numbers of measures employed across all studies, this has been illustrated in Table 4. As seen in Tables 3 and 4, most studies assessing baseline physiological functioning measured a single physiological marker, while three studies (27%) reported the measurement of multiple physiological markers [12, 33, 34]. Cortisol was the most commonly measured physiological marker, with nine studies (82%) employing a

cortisol measure [12, 30, 33 – 39]. All reported measurement of salivary rather than serum cortisol, but there was variation in the type of cortisol measures employed, with four different cortisol measures reported. The cortisol awakening response was most common, and was included in seven (78%) of the studies that reported on cortisol [12, 30, 33 – 36, 38]. This was followed by awakening cortisol in six (67%) studies [12, 30, 33, 34, 38, 39], cortisol at specific timepoints in four (44%) studies [12, 33, 34, 38, 39], and diurnal rhythm in three (33%) studies [30, 36, 37]. Finally, three studies (27%) that reported on baseline physiological functioning measured salivary alpha-amylase [12, 33, 34].

(Insert Table 4 about here)

Cardiovascular measures were reported in five (46%) studies [12, 33, 34, 40, 41,]. Three (60%) of these [12, 33, 34] reported use of ambulatory blood pressure and heart rate measurement, while one used ambulatory measures to calculate heart rate variability [34]. Another study reported use of an electrocardiogram and heart rate monitor to measure heart rate variability [41]. Finally, one study reported obtaining a single laboratory measurement of blood pressure [40].

Physiological Outcomes

Cortisol. Overall, findings from the nine studies that reported on baseline cortisol levels suggest potential cortisol dysfunction, with eight of these studies (89%) reporting blunted cortisol responses for at least a subset of participants. Three studies (33%) found that cortisol levels of parents of children with ASD were lower than expected for healthy adults [30, 33, 34]. Diurnal cortisol rhythm among parents of children with ASD was also found to be lower compared to parents of typically developing children [36] or for a subset (13.4%) of parents of children with ASD [37]. Lower cortisol was predicted or associated with high parental resilience [38] and higher reported negative life events [39], while one study found *higher* cortisol awakening responses following recent exposure to stress for parents who did not report negative life events. Similarly, one study found that parents of children with ASD had significantly *higher* cortisol awakening responses than parents of typically developing children when controlling for negative affect [35]. Finally, one study [12] reported that parents of children with ASD had significantly lower cortisol levels 30 minutes after

waking than parents of typically developing children, but no significant group differences were reported for the cortisol awakening response or other individual cortisol measures.

Both participant and care recipient characteristics were identified as potential predictors of cortisol levels. Lower cortisol levels were associated with lower parental cognitive-oriented problem coping [35], lower parent-child dysfunctional interactions [30], higher child parasomnias and lower child fine motor skills [33], and higher care recipient self-injury [37]. Additionally, one study reported a significant interaction effect between history of care recipient behaviour problems and daily behaviour problems [36], such that morning cortisol levels among mothers whose children had a history of clinically significant behavioural issues showed a less pronounced morning rise compared to those whose children did not have a history of behavioural issues. Limited information was reported on gender differences in baseline cortisol functioning for parents of children with ASD, with one study [30] reporting higher morning and awakening cortisol levels among fathers than mothers of children with ASD, while another study [34] did not detect any significant differences in cortisol responses between mothers and fathers of children with ASD.

Cardiovascular activity. Four out of the five studies (80%) that reported on baseline cardiovascular activity reported cardiovascular activity that was in the normotensive range [33, 34] or did not significantly differ from parents of typically developing children [12, 40]. One study [41] found that parents of children with ASD showed significantly lower resting heart rate variability (indicative of *more* physiological stress) compared to parents of typically developing children.

One study [12] reported that there was no significant correlation between cardiovascular measures and parent-reported distress, anxiety or depression. Higher unmet service needs and parent behavioural disengagement and lower child daytime sleepiness were reported as significant predictors of higher blood pressure among mothers of children with ASD [33], while parental perception of children's lability/negativity was found to significantly predict lower parent heart rate variability [41].

Alpha-amylase. Alpha-amylase levels were not found to differ from expected ranges for healthy adults [33, 34] or levels among parents with typically developing children [12].

Control Group. Control groups of parents of typically developing children were most common, with a total of 341 parents of typically developing children included as control

participants across five (46%) baseline studies [12, 35, 36, 40, 41]. One study [30] included a control group of 49 parents of children with ASD on a waiting list for a service dog. The five (46%) remaining baseline studies [33, 34, 37 – 39] did not include a control group.

Participant Characteristics. Across all 11 studies, the majority of participants (80%) were female. Only two studies (18%) included equal numbers of male and female participants [33, 34], while four studies (36%) included only females in their sample [33, 36, 39, 40]. For the eight papers reporting on participants' age, the mean age of participants was 45.2 years. Two papers [37, 40] did not report mean age, while age for parents of children with ASD could not be separated from the control group in one study [30]. Only three studies [33, 40, 41] reported age range, with an overall participant age range of 20-65 years.

Care Recipient Characteristics. As shown in Table 3, one study [40] did not report on care recipient gender. For the remaining 10 studies, the majority of care recipients (79%) were male. Only one study [41] reported more female care recipients (64%) than males, while one study [37] reported all male care recipients. For the 10 papers that had data available, the mean age of care recipients was 12.6 years. One study [40] did not report mean age for care recipients. The overall age range of care recipients was 2-53 years across the seven studies that reported these data [30, 33, 35 – 37, 40, 41].

Setting. Only one baseline study [40] was conducted in a laboratory setting, with all others (91%) conducted in home settings.

Methodological Quality. Following exclusion of lower quality studies, five (56%) studies that reported on measurement of baseline cortisol levels remained [12, 33, 34, 35, 38]. The pattern of results was relatively unaffected, with the percentage of studies reporting blunted cortisol levels for at least a subset of participants reducing only slightly from 89% to 80%. Most predictors of baseline cortisol levels remained, with higher child parasomnias, lower fine motor skills [33] and lower cognitive-oriented problem coping [38] associated with lower cortisol levels for parents of children with ASD.

The overall pattern of results in relation to baseline cardiovascular activity was also relatively unchanged. Four of the five studies remained (80%), with all remaining studies reporting that parents of children with ASD either had cardiovascular activity within the normotensive range [33, 34] or that

did not significantly differ from parents of typically developing children [12, 40]. The results in relation to salivary alpha-amylase were not affected, with all studies that reported measurement of baseline salivary alpha-amylase levels [12, 33, 34] remaining after the exclusion of lower quality studies.

Physiological Reactivity

Data for studies that measured physiological reactivity to stress are presented in Table 5.

(Insert Table 5 about here)

Physiological Measures. As shown in Tables 4 and 5, a variety of different measures were used across the studies, with all incorporating measures obtained before, during and after the presentation of a psychosocial stressor. Most studies measured a single physiological marker, while only one study reported measurement of two physiological markers [11]. Salivary cortisol reactivity was reported in two (50%) studies [11, 42], while salivary immunoglobulin-A reactivity [42], heart rate and heart rate variability [43], and electrodermal activity [21] were each reported in one study.

Physiological Outcomes

Cortisol. As shown in Table 5, there was evidence of lower cortisol levels for some but not all participants in the two studies that reported on measurement of cortisol reactivity to stressors. One study [11] found that cortisol levels were significantly lower at all time points during the stress reactivity test for parents of children with ASD compared to parents of typically developing children, although the groups did not differ in the *magnitude* of their cortisol responses to the stressor. The other study [42] reported blunted cortisol response to acute stressors for parents of *adolescent* and *adult* care recipients, but not for parents of *child* care recipients with ASD. Both studies [11, 42] explored predictors relating to age and/or time spent in the caregiving role, with higher caregiver burden and care recipient age associated with lower cortisol responses [11]. Conversely, the number of years caring for the care recipient was positively correlated with cortisol levels for caregivers of adolescent and adult care recipients with ASD [42].

Salivary immunoglobulin-A. One study reported on measurement of salivary immunoglobulin-A reactivity [11], which was found to be significantly lower for parents of children with ASD compared to parents of typically developing control group during and after exposure to the stressor. The immunoglobulin-A response was also found to *decrease* for the ASD group, while it increased for the control group. In this study [11], lower immunoglobulin-A levels were associated with higher levels of worry regarding the care recipient's future and lower reported somatic symptoms among parents of children with ASD.

Heart rate variability. Heart rate and heart rate variability reactivity were reported in one study [43], with findings of lower sympathetic reactivity to stress among parents of children with ASD compared to parents of typically developing children. Higher sympathetic activity was correlated with higher somatic symptoms reported by parents of children with ASD.

Electrodermal activity. One study [21] reported on measurement of electrodermal activity in response to acute stress, which was found to be weaker for parents of children with ASD compared to parents of children without ASD. For parents of children with ASD, higher electrodermal activity in response to stress was associated with higher parent-reported somatic symptoms and negative mood.

Control Group. Control groups consisting of parents of typically developing children were also most common in the reactivity studies, with a total of 107 parents of typically developing children included as control participants across three (75%) reactivity studies [11, 21, 43]. One study did not include a control group, but conducted comparisons between parents of child, adolescent, and adult children with ASD [42].

Participant Characteristics. Across all four studies, there was a relatively even distribution of male and female participants, with a slight majority of female participants (64.6%). Mean age of participants was 45.6 years, with no study reporting age ranges for participants.

Care Recipient Characteristics. The majority of care recipients (84.8%) across all studies were male. The mean age of care recipients was 13.8 years, with no study reporting age ranges for participants. However, De Andres-Garcia et al. [42] compared parents of child, adolescent and adult children with ASD, suggesting a spread of ages within this study.

Setting. All four studies were conducted in laboratory settings.

Stressor. All four studies reported employing a psychosocial stressor and inclusion of a video camera during the stressor. Two (50%) studies [11, 42] reported use of an adapted version of the Trier Social Stress Task [44], while the other two studies (50%) reported using the Stroop test, mirror-drawing test and an arithmetic task [21, 43].

Methodological Quality. The exclusion of lower quality studies appeared to have minimal impact on the pattern of results for studies that reported on physiological reactivity to stressors. For cortisol reactivity, only one of the two studies (50%) that reported measurement of cortisol reactivity to stressors remained [11] following exclusion of lower quality studies, with cortisol found to be significantly lower for parents of children with ASD than parents of typically developing children across all assessed time points. The results in relation to salivary immunoglobulin-A, heart rate variability and electrodermal activity were not affected, with all studies that reported measurement of these physiological indices [11, 21, 43] remaining after the exclusion of lower quality studies.

Discussion

Research focused on self-report measures has consistently identified high levels of psychological distress among parents of children with ASD. Such data emphasise the need for objective measurement of stress and health in this population. This paper aimed to (1) identify the types of physiological measures employed within the body of literature, and (2) to synthesise outcomes of physiological measurement of stress among parents of children with ASD. A quality rating was also applied. Fifteen studies published between the years 2010 and 2017 were identified, 11 of which examined baseline physiological functioning and four of which examined physiological reactivity to an experimental stressor. Salivary measures, particularly cortisol, were most commonly employed. The findings in the present review suggest that parents of children with ASD may exhibit HPA-axis and ANS dysfunction, with a pattern of lower physiological activity and reactivity beginning to emerge within the literature for some, but not all, parents of children with ASD.

Physiological Measures Employed

There was considerable variability across the 15 included studies in the types of physiological indices, measures and analyses reported. Salivary measures were the most commonly employed

within this body of literature. In particular, salivary cortisol was reported in 73% of the included studies, though five different indices of cortisol were used. Salivary measures of ANS activity were less commonly reported, with salivary alpha-amylase included in only 20% of studies and salivary immunoglobulin-A reactivity in just one study. No studies assessed antibody responses to vaccination, which were previously found to be poorer among caregivers of children with developmental disabilities (not exclusively ASD) compared to a control group of parents of typically developing children [45]. Only 40% of studies included a measure of cardiovascular activity, despite the strong established links between chronic stress and cardiovascular disease [27, 29]. Additionally, reactivity to stress was somewhat under-represented, accounting for only 27% of the overall studies. This suggests that a number of physiological indices have yet to be fully explored among parents of children with ASD.

These trends in the types of physiological measures employed may at least partly be due to practical considerations. Saliva samples can be obtained relatively non-intrusively from participants, and cortisol has a more established research base in comparison to other salivary biomarkers. Furthermore, measuring baseline physiological functioning is less demanding than exposing participants to a psychosocial stressor. Such practical considerations are particularly important when conducting research with this population, given that parents of children with ASD have high care demands and may be unable or unwilling to participate in more intensive research protocols. That said, laboratory-based reactivity studies enable more controlled investigations of stress responses. Thus, efforts to support parents to participate in such studies and to increase the volume of research in this area may be particularly useful in isolating relevant moderator variables (e.g. time spent in the caring role, adaptive coping strategies, care recipient characteristics, etc.). Further research across a broader range of physiological measures could also further understanding of the relationship between stress and health in this population.

Outcomes of Physiological Measurement

With respect to HPA-axis activity, almost all studies that reported on baseline cortisol levels [12, 30, 33, 34, 36 – 39] and both studies that measured cortisol reactivity to an experimental stressor [11, 42] identified low cortisol levels for at least a subset of participants. ANS dysfunction was

identified through blunted immunoglobulin-A [11] and electrodermal responses to stressors [21] among parents of children with ASD. With respect to cardiovascular activity, the only study that measured cardiovascular reactivity to stress identified lower sympathetic reactivity to a stressor among parents of children with ASD compared to parents of typically developing children [43]. Baseline cardiovascular activity was found to be *higher* for parents of children with ASD compared to parents of typically developing children in one study [41], but studies that measured baseline cardiovascular activity generally reported values that were within the normotensive range [33, 34] or that did not differ significantly from parents of typically developing children [12, 40]. Given that parents of children with ASD are known to report heightened psychological stress [8], findings in relation to physiological activity may initially appear contrary to the reactivity hypothesis, which would hypothesise *higher* reactivity indicative of increased cardiovascular disease among those experiencing high levels of stress [28]. However, there is increasing evidence within the stress literature of *blunted* physiological responses among individuals who experience *chronic* stress [46]. Thus, it is important to consider the potential means through which blunted physiological activity may develop for parents of children with ASD.

Blunted physiological activity has been hypothesised to develop as a result of *prior exposure* to psychological stress [46] and has been associated with lower physiological activity across a range of populations, including adults who experienced more adverse life events in childhood [47] and children who previously experienced bullying [48]. Furthermore, chronic stress has been implicated in a number of diseases that are also characterised by low cortisol activity, including posttraumatic stress disorder, chronic fatigue syndrome and fibromyalgia [49]. Thus, blunted physiological responses to stress could be more likely for those who have been parenting a child with ASD for longer or have been exposed to more stressors. This is supported by findings in the present review that blunted cortisol responses to an acute stressor were found for parents of children with ASD who reported higher caregiver burden [11] and care recipient age [11, 42], which likely indicated that the parent had been exposed to chronic stress for a prolonged period of time. Furthermore, history of child behaviour problems appeared to moderate the impact of recent behavioural problems on cortisol levels [36], which is consistent with prior research that has identified a bidirectional relationship between parental

stress and child behaviour problems [50]. Prior exposure to negative life events was associated with blunted cortisol responses to recent stressors [39]. Bitsika et al. [37] demonstrated a potentially usefully means of isolating these variables, through first identifying subgroups according to the type of physiological responding exhibited, and then further investigating the psychosocial variables that differentiate parents within these subgroups. Thus, future research should further investigate different subgroups of physiological responding and associated psychosocial variables among parents of children with ASD.

While it seems likely that blunted physiological activity among parents of children with ASD emerges as a result of chronic exposure to stress, it remains unclear whether it is adaptive or maladaptive for health. Low or blunted reactivity to stress has often been assumed to be unharmed or even protective [46]. Fries et al. [51] hypothesised that blunted cortisol activity may develop as a protective response that reduces the harmful effects associated with repeated cortisol responses to daily stressors, while cardiovascular adaptation to stress can also occur among individuals experiencing chronic stress [52]. Thus, it is possible that lower physiological activity and reactivity among parents of children with ASD serves an adaptive function. This is consistent with findings in the review that lower sympathetic reactivity to stressors was associated with *lower* reported somatic symptoms among parents of children with ASD [21, 43]. Parents of children with ASD who have been exposed to chronic stress potentially develop more adaptive coping strategies, which could alter their perceptions and/or their ability to cope with stressors. Previous literature has demonstrated a protective effect of certain adaptive coping strategies [53]. Limited data are available from studies included in this review on the link between coping strategies and physiological outcomes, although Ruiz-Robledillo et al. [38] found that higher resilience was associated with lower cortisol among parents of children with ASD compared to those with lower levels of resilience. However, Ruiz-Robledillo and Moya-Albiol [35] found that cognitive-oriented coping, an active coping strategy typically associated with more positive outcomes, was associated with *poorer* reported health for parents of children with ASD. The authors hypothesised that for parents of children with ASD, the conflict between an active coping style and a situation that they had no control over may have resulted in poorer physical health. Thus, further research is needed to tease out the complex relationship

between individual characteristics and coping strategies that may moderate or mediate the impact of stress related to parenting a child with ASD on physiological outcomes. This could point to future avenues for intervention to improve quality of life for this population.

However, while it is possible that lower physiological activity could serve an adaptive function for parents of children with ASD, there is also potential for it to have long-term negative health implications. Fries et al. [51] hypothesised that while blunted cortisol activity might initially serve a protective function for an individual, it can affect homeostatic balance and in turn contribute to side-effects and health problems such as symptoms of pain, fatigue, high stress sensitivity, and decreased immunity [51]. Recent research suggests that reactivity at both high and low extremes is likely to be maladaptive for health. While data available in the present review regarding links between physiological activity and parent-reported health suggest positive associations, it should be noted that many studies did not explore the relationship between these variables. Furthermore, both extremes (i.e. high and low reactivity) have been linked to different negative health outcomes, with *high reactivity* linked to cardiovascular disease, while *low reactivity* has been linked to other outcomes such as obesity, addiction, and depression [46]. However, many outcomes relevant to low reactivity were not assessed within the literature included in the present review. Thus, future research among parents of children with ASD is needed regarding the implications of low physiological activity for health, with the inclusion of a broader array of health-related outcome measures. This could further our understanding of whether low physiological activity in this population is adaptive or maladaptive for health, which would have important implications for its management and treatment.

While blunted physiological responses may reflect reduced physiological capacity in response to stress, it has also been hypothesised that physiological responses to stress could potentially be counterbalanced by competing physiological demands that arise from emotional or bodily factors such as sleep [46]. This is an important consideration in relation to parents of children with ASD, given the known sleep problems experienced by individuals with ASD [54]. Up to 80% of parents have reported erratic sleep patterns among their children [55], and sleep problems have been identified as a source of parenting stress for parents of children with ASD [56]. In the present review, one study reported that higher child parasomnias among care recipients were associated with lower morning cortisol

among mothers of children with ASD [33]. Thus, it is possible that tiredness may present a competing physiological demand for parents of children with ASD, which counterbalances other physiological responses to stress such as cardiovascular and cortisol responses [46]. Additionally, tiredness related to the care recipient's sleep issues could interfere with the parent's compliance with the experimental protocol, particularly for home-based studies. However, many studies included in this review did not measure parent or care recipient sleep problems. Given the high levels of sleep issues present among individuals with ASD, further research is needed to explore the relationship between child sleep issues and parent physiological activity, by considering multi-system analyses of physiological stress responses within this population. Furthermore, if future research establishes a link between child sleep issues and parent physiological stress responses, this would indicate an important avenue for intervention that could potentially improve quality of life and health outcomes for parents as well as individuals with ASD.

Limitations

This systematic review was limited in a number of ways. The exclusion of grey literature may have led to a 'file drawer' effect reflective of bias towards publication of positive results. However, it was felt necessary to include only studies that had been through rigorous peer review. Furthermore, it is notable that some studies identified in the review did in fact report on non-significant findings [12, 40]. Additionally, the review could be critiqued for utilising an adapted quality rating measure that has only been used in one published study. However, extensive review of the literature did not identify any other tool that was suitable for applying with studies that measured both baseline physiological functioning and physiological reactivity to a stressor. Despite these limitations, the review provides an important foundation for future research in this area. We believe that the assessment of methodological quality is a strength of the current study. In this review, studies were generally found to be adequate in terms of methodological quality, more so for studies that measured baseline physiological functioning than those that measured physiological reactivity, with average scores of 7.7 (range: 5-12) and 5.25 (range: 4-6), respectively, out of a possible 12 points. The main areas in which both categories of studies scored lowest were on failure to measure extraneous variables relevant to physiological outcomes (e.g. medical or psychological conditions, medication

use, physical fitness, activity levels during procedures) and failure to report effect sizes and confidence intervals. Thus, future research in this area should seek to build upon the methodological rigour of past studies and address weaknesses in the areas of internal validity and statistical conclusion validity in order to further understanding of physiological outcomes for parents of children with ASD through high-quality research.

Implications for Future Research

This research area addresses innovative methodologies for the measurement of parental stress and wellbeing. Consequently, this review has highlighted a number of important future research avenues and design considerations, many of which have been identified throughout this discussion. Other gaps identified in the included studies highlight additional areas for consideration in future research. None of the included studies utilised a control group of parents of children with other disabilities, thus it is not possible to determine the extent, if any, to which physiological responses to stress differ for parents of children with ASD and other disabilities. Indeed, it is possible that these physiological responses are representative of parents of children with developmental disabilities more generally, rather than being unique to parents of children with ASD. Given that parents of children with ASD report significantly higher levels of stress [5] and poorer health [14] than parents of children with other disabilities, it would be of particular interest to explore whether they are more likely to experience dysregulation of the HPA-axis and ANS. Thus, future research should consider the inclusion of control groups of parents of children with other developmental disabilities. It should also be noted that several studies within the review were conducted by the same authors using similar procedures, and it is therefore possible that there was overlap with participants within these studies. Thus, the body of literature is still small and findings should be interpreted with caution. Some studies also found poor correspondence between physiological indices and self-report measures of stress [12] or other physiological indices [33] among parents of children with ASD, meaning that care should be taken when selecting outcome measures to ensure that these are representative. The primary objectives of future research should be to identify the main variables that account for differences in physiological responding across parents of children with autism, and to determine whether low

physiological activity is adaptive or maladaptive for health. Multicomponent analyses are likely to be required in order to tease out these variables.

Conclusion

To conclude, salivary cortisol has been the most commonly employed physiological measure to date. A pattern of blunted physiological activity is beginning to emerge within the literature for parents of children with ASD, though some studies have reported normal or even higher physiological activity among this population. Thus, findings suggest that HPA-axis and ANS dysfunction is likely to be present for some, but not all, parents of children with ASD. Further methodologically robust research is needed to build on the extant literature and to explore individual and care recipient characteristics that may impact on physiological activity among parents. Additionally, further consideration of outcome measures is needed to ensure the range of potential outcomes is being considered and explored. Such research would further elucidate the effects of stress on physiological activity, the health implications, and potential moderating and mediating variables for parents of children with ASD.

Declaration of Interest. The authors report no declarations of interest.

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Table 1. Definitions for coding of physiological measures

Physiological System	Physiological Measure	Study Category	Code	Definition*
HPA-axis	Cortisol	Baseline Physiological Functioning	Diurnal rhythm	Degree of change in cortisol levels from early morning to late evening.
			Cortisol awakening response	Size of the post-awakening surge in cortisol that typically occurs in the 30-45 minutes after waking. Coded as cortisol awakening response if any of the typical calculations were employed (i.e. if this was calculated by deducting the waking cortisol value from the cortisol value 30-45 minutes after waking; or if area under the curve calculations were used).
			Awakening cortisol	Levels taken as soon as possible after waking.
			Cortisol at specific time points	Levels measured at specific times (e.g. 11am) or time points (e.g. morning) throughout the day. Time or time point will be specified (e.g. cortisol 30 minutes after waking).
			Physiological Reactivity	Salivary cortisol reactivity
Autonomic nervous system (ANS)	Cardiovascular	Baseline Physiological Functioning	Ambulatory cardiovascular activity	Baseline cardiovascular activity measured using portable rather than laboratory-based cardiovascular measures, typically across the day. Further coded to indicate whether blood pressure, heart rate and/or blood pressure/heart rate <i>variability</i> were reported following ambulatory measurement.
			Cardiovascular activity (laboratory-based)	Baseline cardiovascular activity measured in a laboratory-based setting, typically from one measure.

			Heart rate variability	Further coded to indicate whether blood pressure and/or heart rate were measured.
	Physiological Reactivity		Cardiovascular reactivity	Any index of heart rate variability reported, including those calculated using electrocardiogram measurement or using a heart rate monitor.
				Any cardiovascular measurement reported before, during and after the presentation of a stressor.
				Further coded to indicate whether blood pressure, heart rate and/or heart rate variability were measured.
Salivary alpha-amylase	Baseline Physiological Functioning		Salivary alpha-amylase	Baseline levels of salivary alpha-amylase measured.
	Physiological Reactivity		None reported	
Salivary Immunoglobulin-A	Baseline Physiological Functioning		None reported	
	Physiological Reactivity		Salivary immunoglobulin-A reactivity	Salivary immunoglobulin-A measured before, during and after the presentation of a stressor
Electrodermal activity	Baseline Physiological Functioning		None reported	
	Physiological Reactivity		Electrodermal reactivity	Electrodermal activity measured before, during and after a stressor.

* Adapted from Adam and Kumari [18]

Table 2. Criteria used to assess the methodological quality of included studies (adapted from Lydon et al. [32])

Category	Criteria
Descriptive Validity	Experimental design is stated
	<p>Sample size is stated</p> <p>The following participant characteristics are outlined:</p> <ul style="list-style-type: none"> (a) Age (b) Gender (c) Any medical/psychological diagnoses/conditions (d) Medication use <p>Background factors which affect physiological responses are measured:</p> <ul style="list-style-type: none"> (a) General physical fitness (b) Affective state during the experimental procedures (c) Physical activity during the experimental procedures <p>The physiological response, and any behavioural responses being measured, are operationally defined</p> <p>* The stimulus/stimuli presented are described in detail including information on their intensity and duration</p> <p>If standardized measures are used, the psychometric properties of these are described</p> <p>Statistical methods employed are outlined</p>
Internal validity	<p>A control group or control condition is utilized</p> <p>If a control group is used, an attempt is made to match the experimental and control group on pertinent variables (defined as age and gender)</p>

	Consideration of potential mediator or moderator variables within analyses is evident
	Background factors that impact physiological responses are controlled for either through procedural consideration or analyses:
	(a) Psychological or medical conditions
	(b) Medication use
	(c) General physical fitness
	(d) Affective state
	(e) Physical activity during experimental session
	* Baseline physiological activity is considered during analyses
	Multiple measures of physiological activity are employed during experimental procedures
External validity	Experimental conditions/stimuli are representative of those which may be encountered in everyday life
Statistical conclusion validity	The statistical significance of findings is examined
	Effect sizes are calculated for findings
	Confidence intervals are calculated for findings
	Analyses appropriate for the research question are utilized
	Individual responding is considered during statistical analyses

* Not applicable for studies that measured baseline physiological functioning.

Table 3. Summary of studies investigating baseline physiological functioning

Study	Control Group	Caregiver Characteristics			Care Recipient Characteristics		Setting	Physiological Measures	Physiological Outcomes
		N	Mean age (SD), range	Gender (% female)	Mean age (SD), range	Gender (% male)			
Aschbacher et al. [40]	Typically developing (n = 37)	31	- 20-50 years	100%	- 2-16 years	Not reported	Laboratory	Cardiovascular activity (blood pressure), laboratory-based	No significant group differences in blood pressure.
Bitsika et al. [37]	None	149	Not reported	90.6%	11.2 years (3.32) 6-18 years	100%	Home	Salivary cortisol (diurnal rhythm)	86.6% parents showed a diurnal rhythm decline in cortisol from morning to afternoon (labelled as DR present), while 13.4% did not (labelled as DR absent). <i>Comparison of DR present and DR absent groups:</i> Significant univariate difference across groups for child aggression to self. Child aggression towards self was significantly higher among the DR-absent group. Aberrant Behaviour Checklist item 50 (<i>Deliberately hurts him/herself</i>) significantly contributed to parents' DR dysregulation in multiple regression analyses.
Costa et al. [41]	Typically developing (n = 41)	37	41.3 years (4.9) 33-55 years	83.8%	9.1 years (2.6) 3-13 years	36.5%	Home	Heart rate variability	<i>Group Differences:</i> ASD group showed significantly lower resting heart rate variability (i.e. more physiological stress) than control group. <i>Predictors:</i> Parenting group and parental perceptions of children's lability/negativity

									significantly negatively predicted heart rate variability, but reappraisal did not.
Fecteau et al. [30] *	Waitlist control (ASD on waiting list for service dog; n = 49)	49	Data cannot be separated from control group	85.7%	6.7 years (-) 5-10 years	80%	Home	Salivary cortisol (cortisol awakening response; awakening cortisol; diurnal rhythm)	At baseline, both groups had a lower cortisol awakening response than expected for healthy adults, resulting in a flat diurnal cortisol profile. <i>Gender comparisons:</i> Fathers had higher morning and awakening cortisol levels than mothers across both groups. <i>Predictors:</i> Parent-child dysfunctional interactions had the most effect on awakening and morning baseline cortisol values, while seasonality also explained awakening cortisol variations for both groups.
Foody et al. [33]	None	74	41.2 years (5.4) 26-65	100%	8.9 years (3.6) 2-17 years	77%	Home	Salivary cortisol (cortisol awakening response; awakening cortisol; cortisol at specific time points – 30 and 45 minutes after waking) Ambulatory cardiovascular activity (blood pressure; heart rate) Salivary alpha-amylase	Mean group cortisol values were significantly lower than averages reported in previous studies for typical healthy adults. Mean group alpha-amylase levels were higher than reported averages, but differences were not statistically significant. Mean group cardiovascular responses fell within the normotensive range. <i>Predictors:</i> Higher child parasomnias significantly predicted a lower cortisol awakening response, while lower fine motor skills significantly predicted a lower magnitude cortisol awakening response. Higher quantity of unmet service needs and behavioural disengagement and lower child daytime sleepiness significantly predicted higher systolic blood pressure, while later detection of a problem significantly predicted higher night-time diastolic blood pressure.

Foody et al. [34]	None	38 (19 mother-father dyads)	41.7 years (5.1)	50%	7.3 years (3.4)	79%	Home	<p>Salivary cortisol (cortisol awakening response; awakening cortisol; cortisol at specific time points – 30 and 45 minutes after waking)</p> <p>Ambulatory cardiovascular activity (blood pressure; heart rate; blood pressure variability; heart rate variability)</p> <p>Salivary alpha-amylase</p>	<p>For mothers, awakening cortisol values did not significantly differ from reported averages, but cortisol values 30 and 45 mins after waking were significantly lower than reported averages. For fathers, awakening cortisol and cortisol 30 and 45 min after waking were significantly lower than reported averages. For mothers and fathers, alpha-amylase levels were higher than reported averages but the difference was not statistically significant. Group mean 24-h systolic blood pressure for fathers slightly exceeded the normotensive range, with 58% fathers falling within the hypertensive range. All other group mean blood pressure and heart rate measures fell within the normal range for mothers and fathers.</p> <p><i>Gender comparisons:</i> Fathers had significantly higher awake blood pressure and heart rate variability, and higher night-time systolic blood pressure variability than mothers. No significant difference between mothers and fathers in relation to other cardiovascular measures.</p> <p>Cortisol awakening response and alpha-amylase levels did not significantly differ between mothers and fathers.</p>
Padden and James [12]	Typically Developing (n = 38)	38	41.6 years (5)	50%	7.3 years (3.4)	79%	Home	<p>Salivary cortisol (cortisol awakening response; awakening cortisol; cortisol at specific time points – 30 and 45 minutes after waking)</p>	<p><i>Group comparisons:</i> No significant differences observed for the cortisol awakening response, but parents in the ASD group had significantly lower cortisol levels 30 min after waking. No significant group differences for alpha-amylase or cardiovascular measures.</p> <p><i>Correlations:</i> No significant correlations found between parent-reported measures of parental distress, anxiety or depression with salivary cortisol, cardiovascular or alpha-amylase measures.</p>

								Ambulatory cardiovascular activity (blood pressure; heart rate)	
								Salivary alpha-amylase	
Ruiz-Robledillo and Moya-Albiol [35]	Typically Developing (n = 54)	53	45.3 years (5) -	62.3%	15 years (4) 7-29 years	93%	Home	Salivary cortisol (cortisol awakening response)	<p><i>Group comparisons:</i> When controlling for negative affect, the magnitude of the cortisol awakening response was significantly higher for the ASD group.</p> <p><i>Predictors:</i> Only cognitive-oriented problem coping was a significant predictor of the cortisol awakening response, accounting for 3% of the variance.</p>
Ruiz-Robledillo et al. [38]	None	67	45.5 years (6.6) -	60%	14 years (4.8) -	88%	Home	Salivary cortisol (cortisol awakening response; awakening cortisol; cortisol at specific time points – 30, 45 and 60 minutes after waking)	<p>Resilience was negatively correlated with individual cortisol measures.</p> <p>Resilience was a significant negative predictor of the cortisol awakening response (but not of the magnitude of the cortisol response), accounting for 33% of the variance.</p> <p>Significant differences found between low resilience caregivers and medium and high resilience caregivers, with low resilience caregivers found to have higher levels of morning cortisol than the other two groups.</p>
Seltzer et al. [36]	Typically Developing (n = 171)	86	53.9 years (8.5) -	100%	24.7 years (7.2) 18-53 years	79%	Home	Salivary cortisol (cortisol awakening response; diurnal rhythm)	Significant difference found in diurnal rhythm, with the ASD group showing significantly lower levels of cortisol at all four time points across the day.

History of behaviour problems or daily behaviour problems did not individually predict the cortisol awakening response. However, the interaction between history and daily behaviour problems was a significant negative predictor of the cortisol awakening response, such that mothers whose child had a history of clinically significant levels of behaviour problems had a less pronounced cortisol awakening response the morning after high daily behaviour problems compared to mothers whose child did not have a history of such behaviour problems.

Wong et al. [39]	None	82	51.4 years (8.4)	100%	22.1 years (7.1)	79%	Home	Salivary cortisol (awakening cortisol)	<p>A significant interaction effect was found between number of daily stressors and the number of negative life events for awakening cortisol levels the next day. Mothers who experienced no negative life events had a positive association between the number of daily stressors (previous day) and awakening cortisol levels. Conversely, mothers who experienced a greater number of negative life events had a negative association (though not statistically significant) between number of daily stressors (previous day) and awakening cortisol levels.</p> <p>No significant association between the stressor <i>severity</i> (previous day) and awakening cortisol level for participants who experienced no negative life events. However, a significant negative association was found between stressor severity (previous day) and awakening cortisol level for participants with a greater number of negative life events.</p>
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* Data were only extracted for the baseline component of the study. *Note.* DR = Diurnal rhythm.

Salivary alpha-amylase	Baseline	Salivary alpha-amylase			
	Physiological Functioning		√	√	√
	Physiological Reactivity	None reported			
Salivary Immunoglobulin -A	Baseline	None reported			
	Physiological Functioning				
	Physiological Reactivity	Salivary immunoglobulin-A reactivity			√
Electrodermal activity	Baseline	None reported			
	Physiological Functioning				
	Physiological Reactivity	Electrodermal reactivity			√

Note: Papers have presented in the same order that they have been listed in Tables 3 and 5 (i.e. alphabetical order).

Table 5. Summary of studies investigating physiological reactivity to an experimental stressor

Study	Control Group	Caregiver Characteristics			Care Recipient Characteristics		Setting	Stressor	Physiological Measure(s)	Physiological Outcomes
		<i>N</i>	Age (mean (SD) , range)	Gender (% female)	Age (mean (SD) range)	Gender (% male)				
De Andres-Garcia et al. [11]	Typically Developing (<i>n</i> = 37)	41	45.7 years (1.1)	65.9%	14.2 years (5.7)	83%	Laboratory	Psychosocial (adapted Trier Social Stress Test with video camera)	Salivary cortisol reactivity Salivary immunoglobulin -A reactivity	When frustration was used as a covariate, ASD group showed significantly lower levels of cortisol in all assessed moments compared to controls. No group differences were observed for the magnitude of the cortisol response to stress. Magnitude of the cortisol response was negatively correlated with caregiver burden and age of care recipient in ASD group. Immunoglobulin-A levels were significantly lower in ASD group than the control group. The magnitude of the immunoglobulin-A response significantly differed between groups, with an increase observed for the control group and a decrease observed for the ASD group. For the ASD group, baseline immunoglobulin-A levels were negatively correlated with worry regarding the future of the care recipient, while immunoglobulin-A levels and severity of the care recipient's diagnosis were significant predictors of somatic complaints. For perceived general health, individual characteristics appeared to be the most relevant for explaining variables among both groups, but only in the ASD group were immunoglobulin-A levels also a relevant factor for explaining variance.

										No significant correlation found between cortisol and immunoglobulin-A levels or the magnitude of the responses in the ASD group.
De Andres-Garcia et al. [42]	None (Comparison of child, adolescent and adult ASD caregiver groups)	38	45.9 years (1.3)	68%	14.5 (0.7)	84.2%	Laboratory	Psychosocial (adapted Trier Social Stress Task with video camera)	Salivary cortisol reactivity	Significant cortisol response to acute stressor for caregivers of child care recipients, but a buffered cortisol response to the stressor was observed for caregivers of adolescent and adult care recipients. Number of years spent caring for the care recipient was positively correlated with cortisol before and after the stressor for caregivers of adolescents and during and after the stressor for adults, but no associations were observed for caregivers of children.
Ruiz-Robledillo et al. [43]	Typically Developing (n = 36)	34	45 years (6.6)	71%	13.6 years (5.9)	85%	Laboratory	Psychosocial (Stroop test, mirror-drawing test and arithmetic task with video camera)	Cardiovascular reactivity (heart rate; heart rate variability)	ASD group demonstrated lower sympathetic reactivity to the stressor than control group. No significant associations between cardiovascular responses and self-reported health for the control group. For the ASD group, a positive correlation was found between sympathetic reactivity and self-reported somatic symptoms at various points in the stress test (i.e. dermatological, genitourinary and neurosensory symptoms).
Ruiz-Robledillo	Typically Developing (n = 34)	30	46 years (7.2)	53%	13.1 years (5.7)	87%	Laboratory	Psychosocial (Stroop test, mirror-	Electrodermal reactivity	The ASD group showed a lower magnitude electrodermal response to stress than the control group.

<p>and Moya-Albiol [21]</p>	<p>drawing test and arithmetic task with video camera)</p>	<p>For ASD group, the magnitude of the electrodermal response to stress was positively correlated with anxiety, tension, cholera, mood and somatic symptoms (i.e. muscular, gastrointestinal and female reproductive symptoms).</p>
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