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Treatments burden in adults with end stage renal disease receiving haemodialysis impact on medication adherence and health related quality of life

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Abstract

Background: Haemodialysis imposes substantial treatment burden, affecting medication adherence and health-related quality of life (HRQoL). This study assessed treatment burden and its associations with these outcomes in adults receiving haemodialysis.

Aim: To assess treatment burden in adults with end-stage renal disease (ESRD) receiving haemodialysis and examine its associations with medication adherence and HRQoL.

Materials and Methods: A systematic search of PubMed, Embase and Scopus was conducted for publications from 2000 to 2026. After deduplication of 290 records, manual screening yielded 37 eligible studies — restricted to systematic reviews, meta-analyses, clinical trials, and Mendelian randomisation analyses involving adults (≥ 18 years).

Results: Treatment burden in haemodialysis patients is multidimensional, encompassing high pill burden, time demands and significant psychological distress. Non-adherence rates reached up to 50%, driven by regimen complexity, depression, and caregiver strain. Physical HRQoL was more severely impaired than mental HRQoL, with fatigue and musculoskeletal symptoms as primary drivers. Longer dialysis vintage correlated with progressive symptom worsening.

Conclusions: Treatment burden in ESRD patients undergoing haemodialysis significantly impairs medication adherence and HRQoL, particularly in physical domains. Integrated, patient-centred strategies, including regimen simplification and psychosocial support, are needed.

1. Introduction

End-stage renal disease (ESRD) represents the final stage of chronic kidney disease and necessitates renal replacement therapy, most commonly in the form of haemodialysis (Kim et al., 2021; Aldabbour et al., 2025). Although haemodialysis is a life-sustaining intervention, it imposes a considerable burden on patients, profoundly affecting their physical, psychological, and social domains of life (Yan et al., 2025). With the global prevalence of ESRD continuing to rise, there is an increasing imperative to optimise care and improve outcomes for this vulnerable population (Liem et al., 2022).

Patients undergoing haemodialysis experience a high level of treatment burden, a multidimensional concept encompassing the responsibility of healthcare and its impact on

patient functioning and wellbeing (Gurung and Devkota, 2025). This burden includes, strict dietary and fluid restrictions, frequent hospital or dialysis unit visits, complex medication regimens which often involves 10 to 19 pills per day (Yan et al., 2025; Bavi Behbahani et al., 2024). Consequently, patients often report a wide range of symptoms such as fatigue, pain, and sleep disturbances, alongside psychological challenges, all of which contribute to reduced health-related quality of life (HRQoL) (Pugi et al., 2022).

A key component of treatment burden in this population is medication burden, driven by the need for multiple pharmacological therapies to manage comorbidities and complications associated with ESRD (He et al., 2024). Polypharmacy and complex dosing schedules can significantly impede patients' ability to adhere to prescribed treatments (Ma et al., 2021). Medication non-adherence remains a common and clinically significant issue among haemodialysis patients, with significant consequence for treatment effectiveness and patient outcomes (Egeolu et al., 2023).

Treatment burden in haemodialysis patients is closely associated with reduced medication adherence. High pill burden, complex regimens, and overall treatment demands frequently contribute to non-adherence, leading to worsened clinical outcomes such as hyperphosphataemia, cardiovascular complications, and increased hospitalisations (Kalra et al., 2024).

This elevated treatment burden and suboptimal adherence, in turn, exert a substantial negative impact on HRQoL. Patients commonly experience diminished physical functioning, heightened symptom burden, and psychological distress, resulting in lower scores across multiple HRQoL domains (Rohmah et al., 2024).

Key contributors to treatment burden include polypharmacy, dietary and fluid restrictions, time spent on dialysis, and psychosocial factors (Gurung and Devkota, 2025; Worboys et al., 2025). Although interventions such as structured exercise or patient education show potential in alleviating certain aspects of burden and improving adherence or HRQoL, their integrated effects remain insufficiently explored (Kalra et al., 2024).

Despite increasing recognition of treatment burden as a key patient-reported outcome, few studies have concurrently examined its relationships with medication adherence and HRQoL in adults on maintenance haemodialysis. Existing research often addresses these elements in isolation rather than as interconnected factors (Dumaine et al., 2023).

Aim of the work

The aim of the present study is to assess the level of treatment burden in adults with end-stage renal disease receiving haemodialysis and to examine its associations with medication adherence and HRQoL.

By addressing this gap, the findings may support the development of targeted interventions to reduce treatment burden, enhance adherence, and improve patient-centred outcomes in this population.

2. Materials and methods

A comprehensive literature search was conducted using the electronic databases: PubMed, Embase and Scopus to identify relevant studies on the patients with chronic kidney diseases treated with haemodialysis, with particular focus on medication adherence and quality of life. The following keywords were used individually and in combination: "end-stage renal disease", "end-stage kidney disease", "ESRD", "ESKD", "hemodialysis", "treatment burden", "medication adherence", "health-related quality of life", "HRQoL".

The main search scope covered publications from 2000 to 2026, with particular emphasis on recent articles (2020-2026). Additional search filters applied: studies limited to human subjects and adults (≥ 18 years), no animal studies were included. Only systematic reviews, meta-analyses, clinical trials, Mendelian randomization analyses were taken into account. Articles, published in any other language than English or without English translation available, were excluded.

After automatic elimination of duplications, a total of 290 records were identified from the electronic databases. Then manual screening completed by the authors, narrowed the sources to 37 publications, which applied adequately to the topic.

3. Results

3.1. Conceptualisation of Treatment Burden in End Stage Renal Disease

Treatment burden in adults with ESRD can be defined as a complex, multidimensional construct encompassing psychological, physical, organizational and socioeconomic demands imposed on patients by the long-term need to adhere to a complex treatment regimens (Li et al., 2024).

Haemodialysis, although life prolonging, is associated with a substantial treatment burden and may reduce overall well-being, reflecting a fundamental tension between survival and quality of life. While it extends survival, it can simultaneously diminish patients' overall well-being. In contrast, conservative care – focused on pain management, as well as psychological, emotional and palliative support - is characterized by a lower treatment burden and prioritizes the improvement of quality of life. However, from a strictly medical perspective, it may be considered less effective in prolonging survival (Abu Hatoum and Sperling, 2024).

3.2. Components of Treatment Burden in Haemodialysis Patients

A dominant component of treatment burden in patients with ESRD is the substantial time commitment required for haemodialysis. Typically lasting 3-4 hours per session, multiple times per week, haemodialysis significantly reduces patients' work capacity and impacts daily functioning. Consequently, it can negatively affect economic stability, independence and social roles, with financial strain being particularly pronounced among patients who are family breadwinners (Abu Hatoum and Sperling, 2024; Lin and Chu, 2022; Sharif-Nia et al., 2024).

Psychological burden represents another critical dimension of ESRD treatment. Patients frequently exhibit strong emotional responses, including fear, anger, denial and depression, with dialysis often perceived as a „life sentence“. This burden contributes to treatment avoidance, delayed initiation and reduced engagement with care (Attoun et al., 2025; Hajomer et al., 2025; Li et al., 2024; Akhtar and Pienaar, 2025; Alshammari et al., 2025). Depression, in particular, is considered a core component of treatment burden and is negatively correlated with both mental and physical quality of life (Butt et al., 2022). In addition, psychosocial burden – manifesting as stigma, altered self-perception, as well as difficulty accepting chronic illness – further exacerbates patient distress (Paneerselvam et al., 2022).

Haemodialysis is also associated with a wide range of physical symptoms, including fatigue, dyspnoea, edema, thirst distress, gastrointestinal issues and pain, all of which contribute to overall treatment burden (Abu Hatoum and Sperling, 2024; Lin and Chu, 2022; Sharif-Nia et al., 2024). The treatment itself is physically demanding and may lead to frailty and, in some cases, inability to continue therapy (Hajomer et al., 2025; Li et al., 2024), Akhtar and Pienaar, 2025).

Beyond symptoms, the complexity of the therapeutic regimen further intensifies treatment burden. Patients must adhere to strict dietary restrictions, fluid limitations, polypharmacy and regular dialysis sessions (Sharif-Nia et al., 2024; Attoun et al., 2025). Pill

burden represents a central component of treatment burden in patients undergoing haemodialysis. Phosphate binders alone may account for approximately half of daily medications, with patients often taking a median of around 19 tablets per day. Such regimen complexity is a well-established risk factor for non-adherence in chronic disease management (Wang et al., 2014; Gray et al., 2019; van den Oever et al., 2025).

Treatment burden also extends beyond the patient and is indirectly mediated through caregivers. Caregivers play a crucial role in enabling adherence, managing logistics such as transport and scheduling, and supporting daily medical routines. This implies that treatment burden is partially transferred from patient to caregiver, creating a shared burden system (Driehuis et al., 2025).

Overall, treatment burden in hemodialysis patients is inherently multidimensional, encompassing interrelated physical, psychological and organizational demands that collectively impair daily functioning and health-related quality of life (Alshammari et al., 2025).

Importantly, certain protective factors may buffer against high treatment burden. These include patient education, family support, maintaining healthy weight and urban residence with better access to healthcare resources. These factors may improve self-efficacy and coping capacity (Attoun et al., 2025).

Differences in how patients experience treatment burden are also evident. High-burden patients tend to show poor adaptation to treatment routines, negative illness perceptions, weak social support and limited coping strategies. In contrast, low-burden patients are more likely to reframe their illness positively, maintain routines and social roles, and use adaptive coping strategies (Boehmer et al., 2021).

3.3. Relationship Between Treatment Burden and Medication Adherence

The high treatment burden in patients with ESRD often results in reduced adherence. Multiple mechanisms lead to this result. High treatment complexity generates cognitive and behavioral overload, while side effects and unpleasant medication characteristics contribute to intentional non-adherence. In addition, symptoms such as fatigue, thirst distress and itching reduce patients' capacity and motivation to comply. This aligns with a behavioral capacity model: when treatment burden exceeds patient capacity, adherence declines (Sharif-Nia et al., 2024; Li et al., 2024; Alshammari et al., 2025).

Medication adherence appears to be more strongly influenced by treatment than by patient knowledge alone, indicating that simplifying therapeutic regimens and reducing overall burden may be more effective than education-based interventions alone (van den Oever et al., 2025). Some studies show that patients may postpone initiation of dialysis despite medical recommendations, which can lead to severe complications and emergency hospitalizations. These factors increase mortality risk and overall healthcare burden (Lin and Chu, 2022). Additionally, some patients demonstrate a preference for alternative therapies, such as herbal or folk medicine, often driven by distrust or misunderstanding of conventional medical treatment (Lin and Chu, 2022). These behaviors are consistent with non-adherence to prescribed treatment and may result in the substitution of evidence-based therapies with ineffective alternatives, potentially worsening clinical outcomes. Reported rates of non-adherence are substantial, reaching up to 50% or higher in some populations (Sharif-Nia et al., 2024; van den Oever et al. 2025). Polypharmacy and medication-related problems remain central drivers of non-adherence, making pharmacotherapy management a critical intervention target (Paneerselvam et al., 2022).

A clear inverse relationship exists between pill burden and adherence. Higher pill burden is associated with lower medication possession ratio and an increased likelihood of treatment gaps. This relationship can be explained by cognitive overload related to managing complex regimens, declining motivation over time, and practical inconvenience — particularly given that certain medications, such as phosphate binders, must be taken with meals, further complicating daily routines (Wang et al., 2014; Gray et al., 2019).

Treatment burden also affects adherence indirectly through its impact on patient engagement. When patients are actively engaged, adherence improves, clinical outcomes are better, and hospitalization rates decrease. Conversely, patients overwhelmed by treatment complexity or psychological distress are less likely to participate in decision making and may follow treatment passively rather than meaningfully (Abu Hatoum and Sperling, 2024).

A symptom-treatment burden cycle is often observed in haemodialysis. Increasing symptoms (e.g., fatigue, thirst distress, breathlessness) lead to reduced treatment adherence, which worsens the clinical condition and further intensifies symptoms. This creates a negative feedback loop that progressively diminishes both quality of life and adherence (Sharif-Nia et al., 2024; Gebrie et al., 2023).

Self-management plays a central mediating role in this process. Poor self-management is associated with increased treatment burden and lower adherence, whereas effective self-management can transform complex treatment into manageable routines (Li et al., 2024). Mental health further amplifies this relationship. Anxiety and depression reduce self-efficacy, impair disease control and weaken self-management capacity. This interaction forms an additional negative feedback loop, in which increased symptom burden exacerbates psychological distress, further weakening patients' ability to cope effectively (Attoun et al., 2025; Li et al., 2024).

Treatment burden and adherence are also shaped by demographic factors, particularly age. Older patients tend to be more passive and prioritize end-of-life quality, whereas younger patients are generally more autonomy-driven and focused on maintaining independence (Abu Hatoum and Sperling, 2024).

Finally, adherence is influenced not only by patient-level factors but also by caregiver burden. Increased caregiver strain and reduced well-being are associated with impaired medication adherence, as emotional exhaustion and fatigue may limit caregivers' ability to provide effective support. This highlights that treatment burden in hemodialysis is not solely an individual phenomenon but a shared burden distributed across the patient-caregiver dyad (Driehuis et al., 2025).

3.4. Health-Related Quality of Life in ESRD Patients

HRQoL in patients with ESRD is highly sensitive to both symptom burden and treatment adherence. It is negatively affected by the direct impact of symptoms and the overall treatment burden, while adherence represents a key modifiable factor that can improve patient outcomes (Sharif-Nia et al., 2024; Butt et al., 2022). However, no strong effect was observed on mental HRQoL due to better adherence, indicating different determinants for psychological outcomes (Butt et al., 2022). Furthermore, greater treatment intensity – particularly increased frequency and duration of dialysis – has been paradoxically associated with poorer HRQoL, likely reflecting greater disease severity and cumulative burden (Gebrie et al., 2023).

Haemodialysis negatively affects HRQoL through multiple pathways, including physical symptoms (e.g., fatigue, breathlessness, edema), emotional distress, loss of autonomy, and social and occupational limitations (Lin and Chu, 2022; Gebrie et al., 2023). More broadly, it imposes a substantial multidimensional burden – encompassing time demands, psychological strain, financial pressure and physical exhaustion – which significantly reduces perceived

quality of life. Emotional distress, cognitive overload and poor illness understanding further contribute to reduced HRQoL (Akhtar and Pienaar, 2025, Driehuis et al., 2025). The psychosocial stress, which consists of loss of independence, family burden perception and social disruption, additionally impair the mental health component of HRQoL (Gebrie et al., 2023).

Several validated instruments are used to assess HRQoL in ESRD populations. The Kidney Disease-Targeted Areas (KDTA) scale is a component of the Kidney Disease Quality of Life Short Form (KDQOL-SF™ 1.3) and evaluates kidney disease-specific aspects of quality of life. It includes 11 dimensions, such as: symptoms and discomfort, impact on daily life, disease burden, work status, cognitive function, social interaction, sleep quality, social support and patient satisfaction (Li et al., 2024). In contrast, the SF-36 (36-Item Short Form Health Survey) is a generic HRQoL scale consisting of 8 domains: physical functioning, role limitations (physical and emotional), pain, general health, vitality, social functioning and mental health (Li et al., 2024).

A clear causal chain links adherence, clinical outcomes and HRQoL in haemodialysis patients. Poor adherence — manifesting as non-compliance with dialysis schedules, medication regimens, or dietary or fluid restrictions — leads to a higher incidence of complications, which in turn negatively affects HRQoL (Attoun et al., 2025). In contrast, better adherence is associated with fewer complications, improved clinical stability, and higher HRQoL. Empirical findings demonstrate that higher adherence correlates with improved KDTA and SF-36 scores, as well as a reduced rates of hemodialysis-related complications (Li et al., 2024).

Interestingly, some evidence suggests that The Mental Component Summary (MCS) scores from the SF-36 questionnaire may exceed the Physical Component Summary (PCS) scores, indicating relatively better preservation of psychological well-being compared to physical functioning. This pattern may reflect the development of adaptive coping mechanisms that support mental resilience. However, these psychological adjustments do not mitigate the substantial physical limitations associated with end-stage kidney disease and haemodialysis, highlighting a persistent imbalance between mental and physical HRQoL (Hajomer et al., 2025) .

Sociodemographic and clinical factors also influence HRQoL. Female patients tend to report lower mental HRQoL compared to males, while higher education levels, better

nutritional status and stronger social support seem to correlate with higher HRQoL (Gebrie et al., 2023).

Overall, there is a clear interdependence between treatment burden, adherence, and HRQoL. Reducing treatment burden may improve adherence, and improved adherence, in turn, enhances clinical outcomes and quality of life, underscoring the need for integrated, patient-centered management strategies (Paneerselvam et al., 2022).

3.5. Impact of Treatment Burden on HRQoL

According to various findings, the adverse impact of treatment burden and the associated symptom burden on the HRQL of patients with haemodialysis (HD) continues to be an indisputable matter. Along with the increase of symptom burden, the decrease of sleep quality and depression can occur, which naturally diminishes the quality of life in HD treatment patients (Taşkın Duman and Karadakovan, 2024). Furthermore, decisions such as when to begin dialysis, whether patients remain employed after the onset of kidney failure, and their ability to stay engaged in family and community life are also strongly impacted by their HRQoL.

HRQoL progressively worsens as kidney function declines, with scores decreasing significantly alongside reductions in eGFR; the greatest level of impairment is observed in patients with stage 5 chronic kidney disease (Sharma et al., 2023). Dialysis vintage, meaning the duration of dialysis, influences negatively the symptoms experienced by patients and their overall well-being, considering that longer dialysis duration was associated with increased symptom burden. In patients with longer dialysis vintage, frequent occurrence of gastrointestinal, musculoskeletal, and neurological symptoms was confirmed by assessing Dialysis Symptom Index (DSI) score. The steady rise in the overall DSI score, along with the increased occurrence of musculoskeletal symptoms such as muscle cramps, indicates that longer durations of dialysis may be associated with a growing symptom burden, possibly driven by chronic inflammation or muscle degradation (Yan et al., 2025).

In regard to the extent to which symptoms interfere with the everyday lives of patients, those undergoing hemodialysis frequently reported persistent fatigue, anorexia, and significant weight loss, all of which severely impacted their routine activities, such as lifting small objects or walking short distances, additionally, worsening muscle weakness and reducing stamina also restricted their mobility, often leading to a sense of dependency. The symptoms like muscle cramps and joint pain forced patients to modify their daily routines and incorporate frequent

rest breaks (Paudel et al., 2025). One of the most persistent and daily occurring symptoms in HD patients is pruritus, particularly uremic pruritus, and it significantly affects their QoL. The prevalence of chronic kidney disease-associated pruritus (CKD-aP) in patients undergoing hemodialysis is considered to be present in from 40 to 70% of them, with 37% experiencing moderate-to-severe itching (Bagherzadeh-Rahmani et al., 2025).

Among dialysis patients across all age groups, the physical HRQoL demonstrates a stronger and more pronounced sensitivity to both the number of symptom and their severity, relative to the impact observed on mental HRQoL. It is worth emphasising that physical HRQoL was more heavily influenced by symptom burden in older patients than in younger patients (with the overall symptom burden score being 28.6% of the variance in physical HRQoL, compared with 18.7%). The symptom burden overall in either group of patients decreased slightly during the first 3 months of dialysis and thereafter stabilised (van Oevelen et al., 2024).

3.6. Interplay Between Medication Adherence and HRQoL

Patients with chronic kidney disease (CKD) often regard prescribed fluid limitations as a considerable source of burden, frequently associating them with heightened anxiety, persistent fatigue, and limitations in social engagement. This is unsurprising given the inherent complexity of renal dietary regimens, which present significant navigational challenges for this population. Additionally, sensation of thirst and dry mouth from such restrictions generate further distress and actively undermine patients' capacity to maintain adherence to fluid guidelines, further exacerbating excessive fluid states. Consequently, patients who demonstrated lower levels of acceptance towards these restrictions reported a greater perceived interference of kidney disease with their daily lives and an overall heightened sense of disease burden (Martin et al., 2025).

There is another correlation with medical adherence that requires additional emphasis, it being patients simultaneously suffering from depression. They demonstrate a reduced likelihood of adhering to prescribed medications, maintaining regular dialysis attendance, and following recommended renal diet, while simultaneously being more likely towards physical inactivity. In light of this, it would be helpful to examine the interconnections between these findings and the prevalence and impact of depression among patients living with CKD (Pugi et al., 2022).

3.7. Modifying and Mediating Factors Influencing HRQoL

A wide variety of factors, from co-morbidities all the way to socio-economic circumstances, have either a beneficial or detrimental effect on HRQoL of HD patients. Comorbidity, for instance, unequivocally reduces Kidney Disease Quality of Life Instrument (KDQOL™-36) domains, with at least one domain being adversely affected in the presence of hypertension, diabetes mellitus, cardiovascular disease, or osteoarthritis, cardiovascular disease being the most negatively impacting on HRQoL in this cohort (Aldabbour et al., 2025). Moreover, nutritional status maintains a significant relationship with every domain of generic quality of life measurement, with malnutrition emerging as the single strongest predictor of deteriorated scores across the kidney disease-specific quality of life instrument (KDQOL-SF) (Bavi Behbahani et al., 2024). Another critical factor severely impacting HRQoL that is broadly acknowledged is the economic status of the patient. The presence of a financial burden due to treatment significantly worsened outcomes in most domains of KDQOL-36 particularly in symptoms and burden of kidney disease (Gurung and Devkota, 2025). Patients with comparatively low household incomes may face substantial financial strain, which could restrict their ability to access optimal care while simultaneously amplifying the indirect economic costs associated with sustaining long-term dialysis treatment (Yan et al., 2025). The status of employment of the patient, directly connected to their financial status, impairs the HRQoL, with the odds of lower HRQoL being two times more likely among unemployed patients than those patients who were employed (Gebrie et al., 2023). Nonetheless, among the factors frequently identified as beneficial were adequate dialysis, physical activity, higher education levels, male gender of a patient, as well as family and marital support (Yan et al., 2025; Aldabbour et al., 2025).

3.8. Interventions to Reduce Treatment Burden

Several interventions have been introduced to reduce the treatment burden, including behavioral and educational support for patients, often aided by technology. Changing patients' daily lifestyle habits, including dieting, is also necessary. The possibility of pharmacological intervention to decrease the symptom burden—which, as aforementioned, has a significant impact on patients' HRQoL—should not be overlooked. One of the methods of interventions to lower the symptom burden and improve comfort level and quality of life of HD patients is video-based training. Video-based studies conducted among HD patients has demonstrated a range of beneficial outcomes following intervention, including enhanced patient knowledge

and more positive treatment attitudes, alongside reductions in depressive symptoms and a decreased incidence of acute complications and associated symptoms. Likewise, self-care, self-management and self-efficacy of HD patients was observed when micro video-assisted health education program was introduced (Taşkın Duman and Karadakovan, 2024).

As mentioned previously, malnutrition is the strongest predictor of worsening outcomes on quality-of-life scales, therefore, targeted dietary interventions have been shown to significantly improve nutritional parameters, such as serum albumin levels and BMI, which are closely associated with both physical and mental well-being in this patient cohort (Bavi Behbahani et al., 2024).

3.9. Gaps in the Literature and Future Research Directions

Significant gaps remain in the existing literature that must be addressed to guide future research directions. Most notably, there is a shortage of longitudinal studies and a lack of standardisation in measuring treatment burden. There is also a pronounced need for interventional studies among haemodialysis patients. To address these deficiencies, forthcoming studies should examine whether multidisciplinary approaches targeting symptom burden translate into measurable improvements in HRQoL, while also longitudinal examination of how individual symptoms evolve over time is warranted, given that certain symptoms may respond more favourably to dialysis than others and may influence HRQoL differently. From a clinical standpoint, care plans that are individually adapted and progressively refined in line with a patient's dialysis vintage can potentially optimise both clinical outcomes and the overall treatment experience, which may improve patient coping strategies. Alongside this, the systematic and routine evaluation of nutritional status using validated instruments is essential to enable the early identification of vulnerable patients and the timely implementation of targeted therapeutic interventions (Yan et al., 2025; (van Oevelen et al., 2024).

4. Conclusions

Treatment burden in haemodialysis patients with ESRD is a multidimensional issue that significantly impairs daily functioning and well-being. High burden—driven by symptoms, time demands, and complex medication regimens—leads to reduced medication adherence through overload and decreased self-management capacity. In turn, lower adherence is associated with worse clinical outcomes and poorer HRQoL, particularly in physical domains. The relationship between burden, adherence, and HRQoL is influenced by psychosocial and demographic factors such as support systems, education, and comorbidities. Interventions that

simplify treatment and enhance support may improve both adherence and quality of life. However, further longitudinal and interventional research is needed to better understand and address this relationship.

Author Contributions

Conceptualization, H.L and W.Wr.; methodology, M.D., W.R. and W.Wd.; validation, W.Wr. and H.L.; formal analysis, A.W. and A.G.; investigation, W.R., H.L. and M.J.; resources, M.C. and A.G.; data curation, W.Wr. and M.D.; writing—original draft preparation, H.L. and A.W. and M.C.; writing-review and editing, W.Wr., A.W., H.L., M.C., J.O. and W.R.; visualization, W.Wr. and W.Wd.; supervision, M.D. and A.G.; project administration, W.Wr. All authors have read and agreed to the published version of the manuscript.

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